



January 18, 2018

Lt. Cdr. Brian Andrews-Shigaki
Office Warfighter Performance S&T Dept
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: Interim Technical Report with SF298 by the National Marrow Donor Program®

Reference: Grant N00014-17-1-2388 between the Office of Naval Research and the National Marrow Donor Program

Dear Lt. Cdr. Andrews-Shigaki,

In accordance with the requirements of the Referenced Office of Naval Research Grant, the National Marrow Donor Program® (NMDP) hereby submits the required Interim Technical Report for the period of October 01, 2016, through December 31, 2017.

Should you have any questions regarding the performance activity of under this Grant, you may contact our Chief Medical Officer – Dennis Confer, MD directly at 763-406-3425.

Please direct any contractual questions pertaining to the Grant to Nancy Poland attention at 763-406-3401 or to npoland@nmdp.org.

Sincerely,

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14. ABSTRACT <u>1. Contingency Preparedness:</u> Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan. <u>2. Rapid Identification of Matched Donors:</u> Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event. <u>3. Immunogenetic Studies:</u> Increase understanding of the immunologic factors important in HSC transplantation. <u>4. Clinical Research in Transplantation:</u> Create a platform that facilitates multicenter collaboration and data management.					
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Development of Medical Technology for Contingency Response to Marrow Toxic Agents

Dennis L. Confer, M.D., National Marrow Donor Program

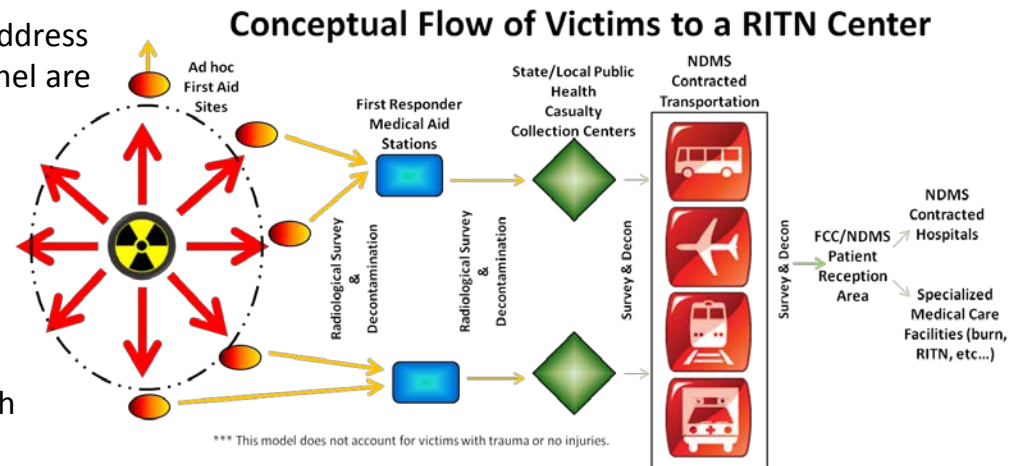


Objective:

- Develop, test and mature the ability of the NMDP to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents

Approach:

- Contingency preparedness through RITN
- Develop science and technology to facilitate the rapid identification of donors
- Conduct immunogenetic research in transplantation
- Perform observational and prospective clinical research in transplantation



Accomplishments:

- Planned table top, regional and functional exercises for execution during the project period.
- Held 6th semi-annual RITN Workshop “Radiological/Nuclear Medical Preparedness: Operationalizing a Decade of Development”
- Added 55,996 minority and 164,691 Caucasian U.S. donors to the Registry
- Published 90 peer reviewed manuscripts and presented 72 abstracts at national/international meetings
- Completed analysis required to integrate an electronic Patient Reported Outcomes (ePRO) system into CIBMTR data collection systems
- Planned and conducted four Data Standards Hackathons that were held in Vienna, Berkeley, Heidelberg and Utrecht

Impact/Transitions:

- Published 90 peer reviewed manuscripts and presented 72 abstracts at national/international meetings
- Added 55,996 minority and 164,691 Caucasian U.S. donors to the Registry

Grant Award N00014-17-1-2388

DEVELOPMENT OF MEDICAL TECHNOLOGY
FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS
MID-YEAR RESEARCH PERFORMANCE REPORT
SUBMITTED JANUARY 17, 2017

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Dennis L. Confer, M.D.

National Marrow Donor Program

N00014-17-2388

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

II. Scientific and Technical Objectives

The main objective of this grant is to develop, test and mature the ability of the National Marrow Donor Program® (NMDP) to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. An accident, a military incident, or terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. Casualties will be triaged by first responders, and those with major marrow injuries who may ultimately be candidates for hematopoietic cell transplantation (HCT) will need to be identified. HCT donor identification activities will be initiated for all potential HCT candidates. NMDP-approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP coordinating center will orchestrate the process to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic and clinical research activities promote studies to advance the science and technology of HCT to improve outcomes and quality of life for the patients.

III. Approach

A. Contingency Preparedness

HCT teams are uniquely positioned to care for the casualties of marrow toxic injuries. The NMDP manages a network of centers that work in concert to facilitate unrelated HCT. The Radiation Injury Treatment Network (RITN), comprised of a subset of NMDP's network centers, is dedicated to radiological disaster preparedness activities and develops procedures for response to marrow toxic mass casualty incidents.

B. Development of Science and Technology for Rapid Identification of Matched Donors

Disease stage at the time of transplantation is a significant predictor of survival, decreasing the time to identify the best matched donor is critical. Methods are under development to rapidly provide the best matched donor for HCT.

C. Immunogenetic Studies in Transplantation

Improving strategies to avoid and manage complications due to graft alloreactivity is essential to improve the outcomes of HCT. Research efforts are focused on strategies to maximize disease control while minimizing the toxicity related to alloreactivity in HCT.

D. Clinical Research in Transplantation

Clinical research creates a platform that facilitates multi-center collaboration and data management to address issues important for managing radiation exposure casualties. Advancing the already robust research capabilities of the NMDP network will facilitate a coordinated and effective contingency response.

IV. Concise Accomplishments

- a. Contingency Preparedness
 - i. Planned table top, regional and functional exercises for execution.
 - ii. Conducted training sessions and tracked training activities at RITN centers.
 - iii. Held 6th semi-annual RITN Workshop “Radiological/Nuclear Medical Preparedness: Operationalizing a Decade of Development”
- b. Development of Science and Technology for Rapid Identification of Matched Donors
 - i. Added 55,996 minority and 164,691 Caucasian U.S. donors to the Registry.
 - ii. Continued accrual to the Temporarily Unavailable Donor (N=107) and Selection, Typing and Transplant (N=43) studies.
 - iii. Planned and conducted four Data Standards Hackathons (DaSH) held in Vienna, Berkeley, Heidelberg and Utrecht.
- c. Immunogenetic Studies in Transplantation
 - i. Completed retrospective HLA and KIR typing on 3619 unrelated donor/recipient pairs.
 - ii. Submitted two manuscripts describing the allogenicity of mismatches outside the antigen recognition domain (ARD) and likelihood of finding an ARD mismatch in unrelated donor transplantation.
- d. Clinical Research in Transplantation
 - i. Completed analysis required to integrate an electronic Patient Reported Outcomes (ePRO) system. This system will enable patients to contribute PRO data directly to clinical studies and other CIBMTR research.
 - ii. Published 90 peer reviewed manuscripts and presented 72 abstracts at national/international meetings during the grant period.
 - iii. Reviewed 204 new study proposals and accepted 797 for discussion at the February 2018 ASBMT/CIBMTR Transplant Tandem Meetings.
 - iv. Twenty one abstracts were submitted and accepted for presentation (9 oral and 12 poster) at the ASH meeting in December 2017.
 - v. Implemented 5 cellular therapy form revisions and developed 3 new forms needed to support a cellular therapies registry.

V. Expanded Accomplishments

Contingency Preparedness

Maintain the Radiation Injury Treatment Network (RITN) to prepare for the care of patients resulting from a hematopoietic toxic event.

Hospitals are eligible to join RITN if they participate in both the NMDP Network of treatment centers and the NDMS. The NDMS is comprised of over 1,800 accredited hospitals across the nation that have agreed to receive trauma casualties following a disaster. The program is managed by the Department of Health and Human Services. RITN conducts targeted recruitment on an annual basis with a goal of expanding the network. RITN consists of 69 transplant centers, 5 donor centers, and 6 cord blood banks (Figure 1).

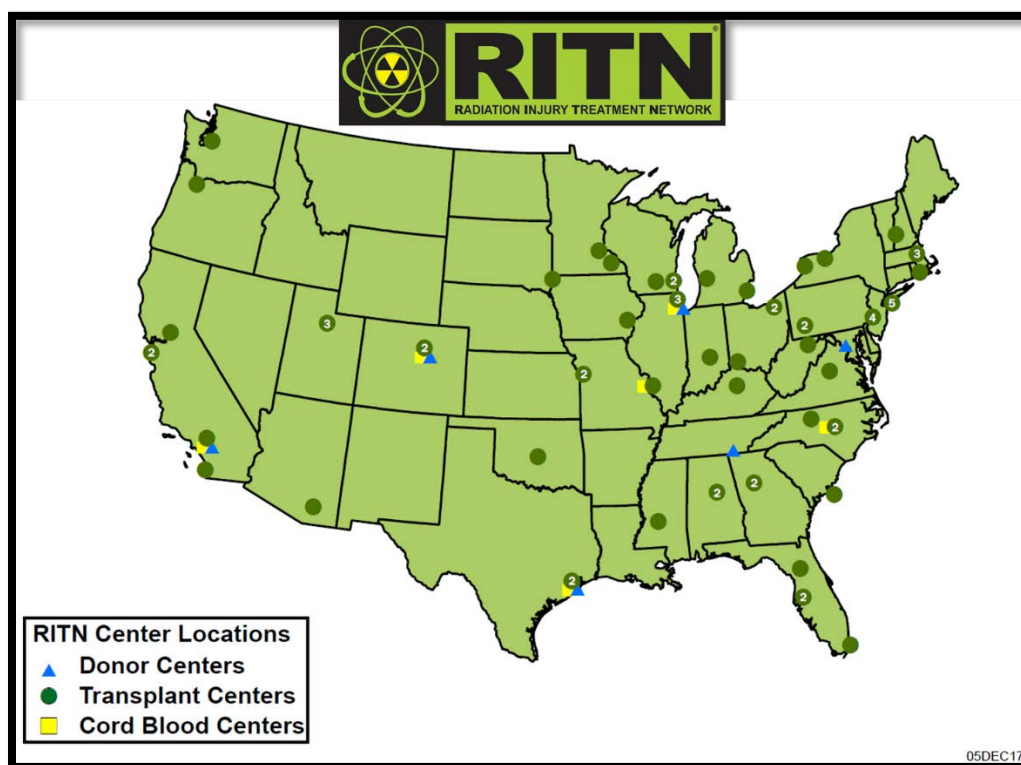


Figure 1. Location of RITN Centers

RITN Preparedness Activities

RITN centers were asked to continue to develop their level of preparedness during 2016-2017. Tasks included communications drills, updating of standard operating procedures, outreach to local public health and emergency management contacts, a tabletop exercise and training of staff.

During 2017, 100% of active RITN centers completed all of their required annual tasks (Figure 2), which is consistent with the performance during previous years.

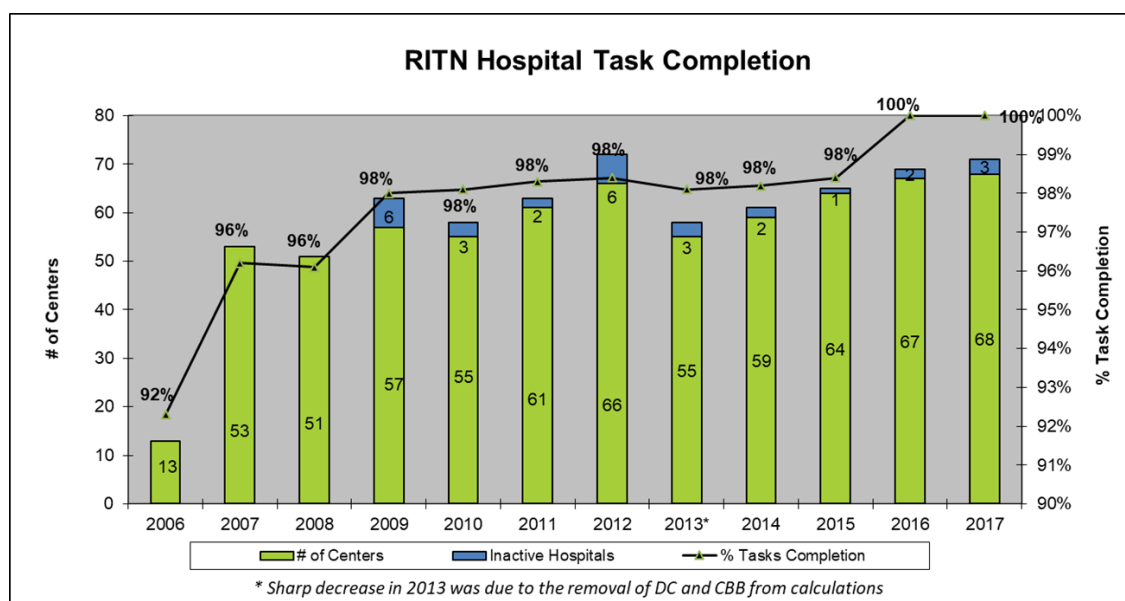


Figure 2. RITN annual training task completion rates by year

- **RITN Exercise Program:** RITN coordinates or provides support for many radiological exercises each year; these include full-scale, functional, regional tabletop and tabletop exercises (the intensity and effort required decreases accordingly from full-scale to tabletop). RITN has facilitated more than
- 650 exercises since 2006 (see Figure 5 for breakdown by type). Activity continued in 2017 with major exercises planned for the next reporting period. Images from a functional exercise conducted by Spectrum Health in Grand Rapids, Michigan in the summer of 2017 are presented in Figures 3 below.

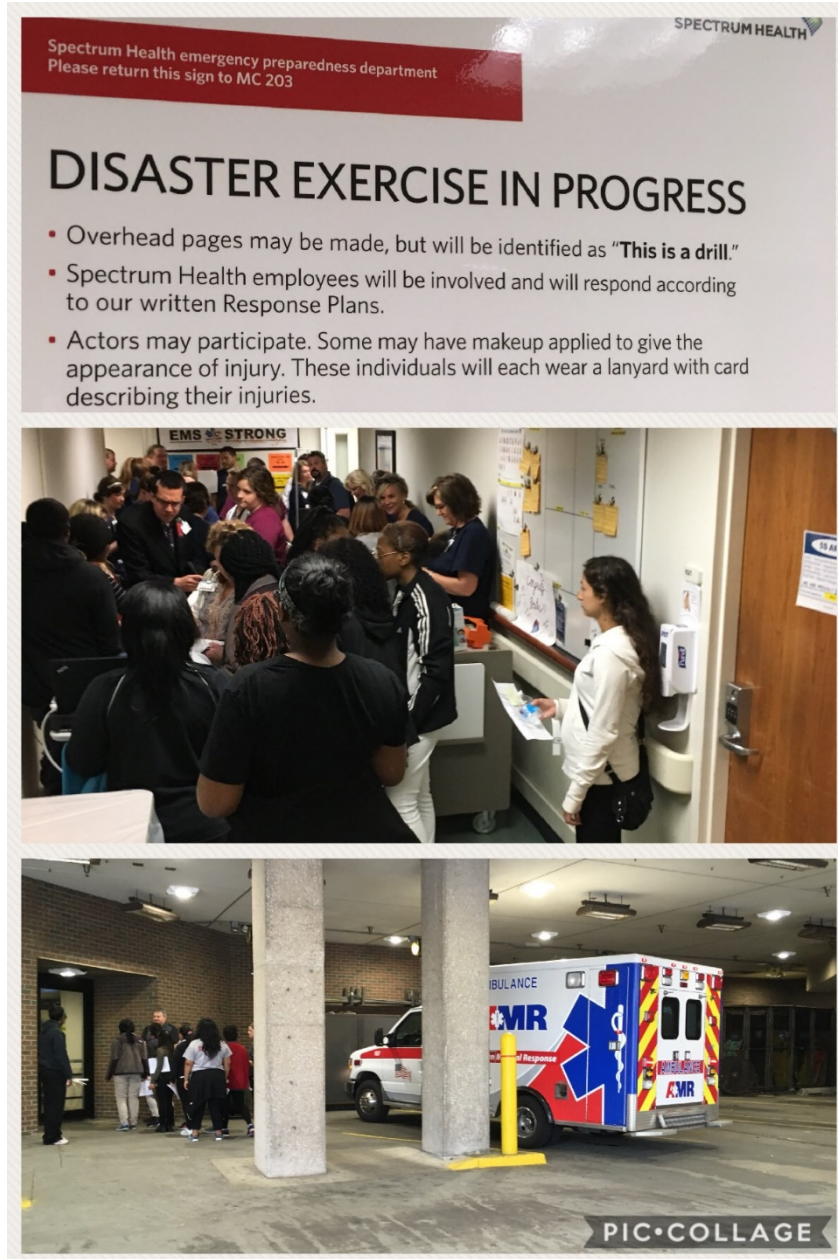


Figure 3: Images from the Spectrum Health's exercise 2017.

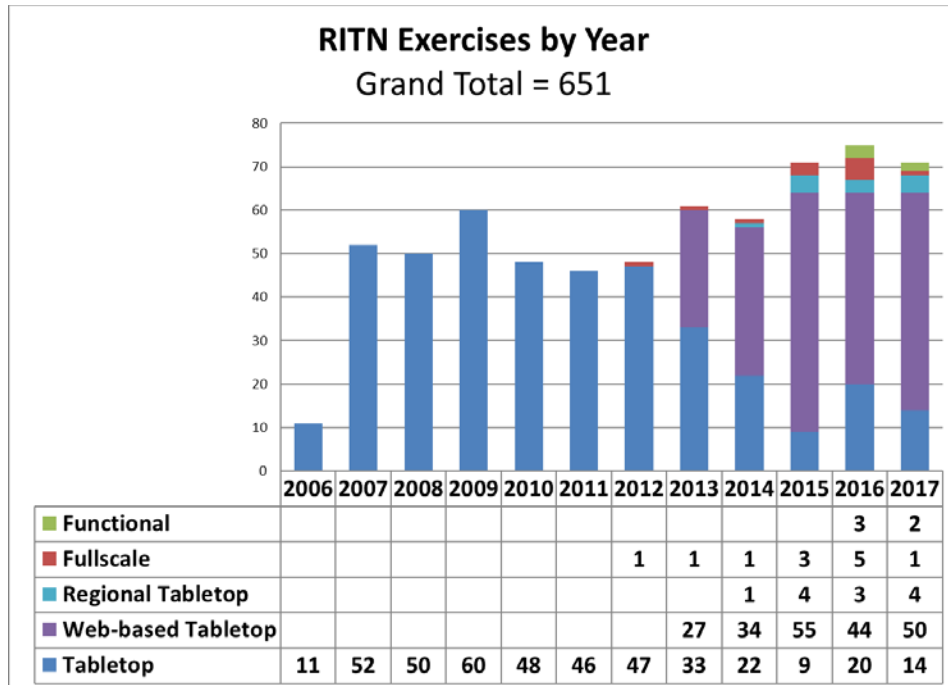


Figure 4. Number of RITN centers participating in exercises by year.

Tabletop exercises

The number of RITN centers participating in tabletop exercises annually is summarized in Figure 4. After Action Reports from all of the 64 tabletop exercises conducted can be found on the RITN website at <https://ritn.net/display.aspx?id=2147484344>. A summary of RITN tabletop exercises conducted to date is provided in Table 1 and the 2017 scenario is illustrated in Figure 5.

Table 1. Summary of annual RITN tabletop exercise scenarios and level of patient surge.

Summary of RITN Tabletop Exercise Scenarios		
Year	Scenario	Max Victims
2006	Radiological Exposure Device (RED) placed on public train system	650 identified as having some level of ARS. 50 patients to each center
2007	Train derailment spills multiple chemicals, produces vapor cloud which exposes a crowd of 15,000	5,000 (mostly children and senior citizens)
2008	IND was detonated and 300,000 victims were triaged	5,000 victims required RITN assistance
2009	10-kiloton nuclear device detonated in a major metropolitan center	12,000 patients with high radiation dose in the 200-600 rad range. 300 patients to each center
2010	Detonation of a surface burst 10-kiloton nuclear device in major metropolitan center	20,000 patients with high radiation dose in the 200-600 rad range. 500 patients to each center
2011	National Disaster Medical System (NDMS) flow and integration	Not specified
2012	1 KT IND detonated 500 miles away from RITN center, 20 patients to prioritize using provided casualty cards	20 casualty cards w/ limited bed availability provided
2013 w/ Webinar Option	Radiological exposure devices placed on mass transit vehicles in multiple US cities	4,500 casualties nationwide; 300 patients and 140 family members are sent to each RITN center
2014 Primarily Webinar	Detonation of a 1KT IND	100 patients from a large metropolitan area 500 miles away
2015 Webinar	Four Radiological Exposure Devices (RED) planted on a university campus	20 adult and 20 pediatric patients with detailed patient profiles and required medical evaluation
2016 Webinar	1 kiloton improvised nuclear device (IND) detonated in a metropolitan area 500 miles away	30 patients (adult or pediatric depending on the hospitals focus) with special emphasis on Family Information Centers to connect patients with their families
2017 Webinar	1 kiloton improvised nuclear device (IND) detonated in a metropolitan area 500 miles away	Reviewed ability to receive inpatients and outpatients for care. Discussion of crisis standards of care and three patients to triage for care.

Exercise Name	2017 RITN Tabletop Exercise (TTX)
Exercise Date	2017
Scope	This exercise is a distance-based tabletop exercise planned for 2 ½ hours. Exercise play is limited to RITN facilities and their response partners' collective challenges and considerations for improved and effective response.
Mission Area(s)	Response
Capabilities	Public Health & Medical Services
Objectives	<p>Objective 1: Hospital staff are able to determine their hospital's capability to receive casualties (inpatient and outpatient) through the National Disaster Medical System (NDMS) following a mass casualty radiological incident.</p> <p>Objective 2: Hospital staff are able to discuss the procedures for implementing Crisis Standards of Care (CSC) at their hospital.</p> <p>Objective 3: Hospital staff are able to describe their approaches for triaging patients and determining initial treatment actions for patients with Acute Radiation Syndrome (ARS).</p>
Hazzard	Radiological
Scenario	Medical surge from a distant radiological incident
Sponsor	<p>Radiation Injury Treatment Network® (RITN)</p> <p>National Marrow Donor Program (NMDP)</p> <p>Office of Naval Research (ONR)</p>

Figure 5. RITN 2017 table top exercise scenario.

RITN Sponsored Full-Scale and Functional Exercises:

During 2017 RITN sponsored one full scale exercises, two functional, and seven regional tabletop exercises, and held six web based RITN tabletop exercises for RITN hospitals. In conjunction with the 2017 Rush University Medical Center functional exercise a video was created to help set the expectations for other RITN hospitals that are interested in conducting such an exercise. With this RITN established a YouTube Channel for RITN related videos. The YouTube Channel can be found by searching for "Radiation Injury Treatment Network" and YouTube or by using to this link: <https://www.youtube.com/channel/UCkd45X1DIPqeRr-u5lph6Og>

The hospitals which conducted an exercise with RITN funding in 2017 are listed in Table 2 below:

Table 2. 2017 RITN Funded Exercises by Hospital and Exercise Type.

Hospital	Exercise Type
Spectrum Health	Full Scale Exercise
Rush University Hospital	Functional Exercise
Massachusetts General Hospital	Functional Exercise
Children's Hospital of Philadelphia	Regional Table Top Exercise (TTX)
Children's Mercy Hospital	Regional TTX
Texas Children's Hospital	Regional TTX
Wake Forest Baptist Health	Regional TTX
University of Arizona Medical Center	Regional TTX
Spectrum Health	Regional TTX
Memorial Sloan Kettering	Regional TTX

Training tasks:

RITN centers are asked to conduct training with the intent to educate and increase the awareness of RITN and its efforts to the appropriate response community. Training options continue to be accessible online at no cost to anyone who is interested. In addition, the in person training option has expanded to include an Advanced HAZMAT Life Support (AHLS) for Radiological Incidents course. As shown in Figure 6 the training options continue to grow, centers can now choose between conducting Basic Radiation Training, having a physician or Advanced Practitioner complete the REAC/TS training, hosting an AHLS course, conducting an Acute Radiation Syndrome Medical Grand rounds session, and having a site assessment conducted. In addition, centers can conduct community outreach and education using the RITN Overview Presentation. All of these materials, with the exception of the REAC/TS training, are available unrestricted, through the RITN website. The RITN web based training catalog includes:

1. Introduction to RITN
2. RITN Concept of Operations
3. GETS 101
4. Satellite telephone 101
5. Basic Radiation Training
6. Non-medical Radiation Awareness Training
7. Radiation Safety Communication Course

The online learning management system allows RITN center staff to complete the full course at their own pace and receive an electronic certificate of completion after meeting all the course objectives and knowledge assessments. Since 2006, RITN has had a hand in the disaster response training or education of over almost 15,000 medical staff affiliated with RITN hospitals.

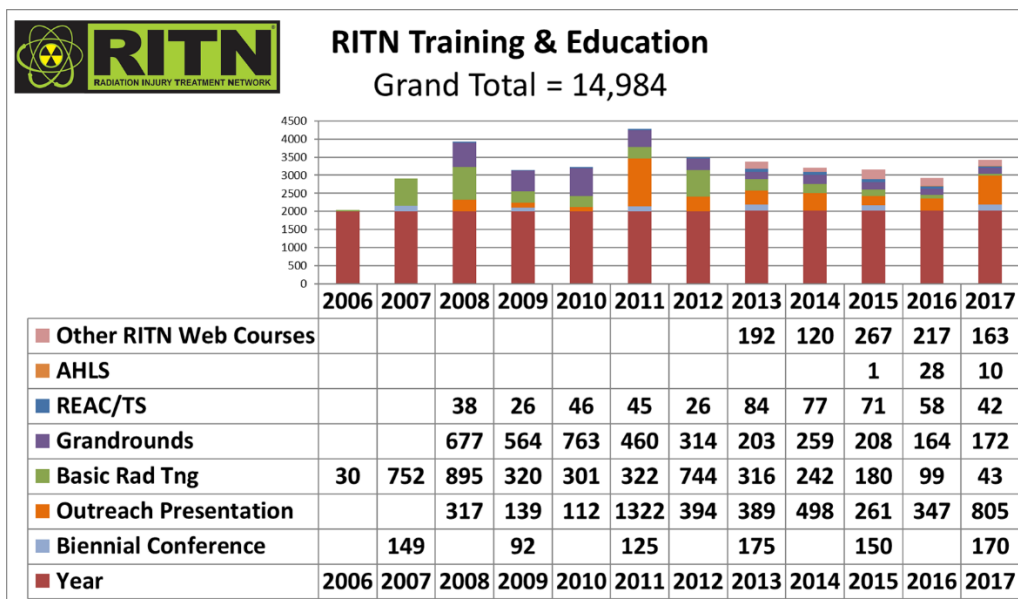


Figure 6. RITN center staff training accomplished by year.

In 2011, RITN initiated the Site Assessment program which has conducted 48 assessments of RITN hospitals (Figure 7). RITN Control Cell staff members review existing documentation at RITN transplant centers using a standardized checklist (Figure 8) to assess overall preparedness. Areas evaluated include Casualty Processing, Outpatient Treatment of Casualties, Inpatient Treatment of Casualties, Coordination with City, State and Regional Assets, and Documentation.

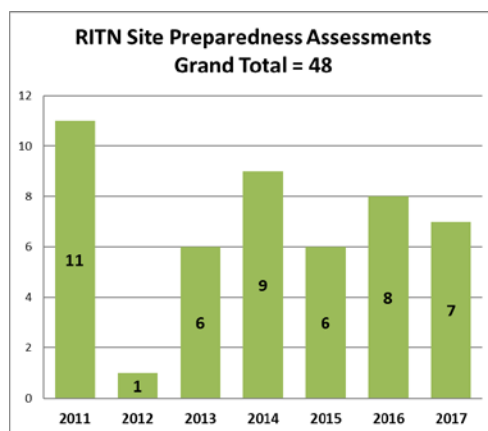


Figure 7. RITN center site assessments by year.

The Site Assessment Checklist formed the basis for revisions to the standard operating procedure (SOP) template that all centers used to update their local SOPs.

The RITN continuously seeks to formalize and develop further partnerships with federal agencies and organizations. In support of this effort RITN conducts outreach through presentations about RITN, and strives to develop new partnerships. During 2017 RITN provided informative presentations to many groups including:

- ASBMT/CIBMTR Tandem Data Managers Conference
- National Council on Radiation Protections
- National Association of City and County Health Officials
- German Medical Defense Conference on Radiation
- FBI Radiation Awareness Work Group in Phoenix
- World Health Organization-Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN) meeting in Geneva
- Dept. of Health and Human Services-Acting Assistant Secretary for Preparedness and Response (DHHS-ASPR) Director of the National Disaster Medical System (NDMS)
- Department of Defense Transportation Command (DOD-TRANSCOM)

To further develop relationships RITN coordinated through its relationship with the Dept. of Health and Human Services-Assistant Secretary for Preparedness and Response RITN participated in the National Level Exercise (NLE) Gotham Shield '17 which was based on a radiological disaster scenario. As part of this exercise RITN was able to successfully transmit bed data of RITN hospitals via the internet directly to the Dept. of Health and Human Services-Assistant Secretary for Preparedness and Response Secretaries Operation Center.

RITN in partnership with the National Library of Medicine Radiation Emergency Medical Management Website (www.REMM.NLM.gov) our Acute Radiation Syndrome Treatment Orders were split into an Adult and Pediatric version, then updated and released on both the REMM and RITN websites.

RITN held the 6th semi-annual RITN educational workshop entitled, “Radiological/Nuclear Medical Preparedness: Operationalizing a Decade of Development”, in Rockville, MD with 165 attendees; highlights included:

- 38 speakers over 1 ½ days
- Opening remarks by Dr. Korch the Acting Assistant Secretary for Preparedness and Response at the Dept. of Health and Human Services
- Biomedical Advanced Research and Development Agency (BARDA) presentation on the Public Health Emergency Medical Countermeasure Enterprise
- FDA presentation about systems to expedite medical countermeasure development
- Center for Medicare and Medicaid presentation about new Emergency Preparedness Rule
- Real world medical mass casualty response case studies from the Pulse Nightclub in Orlando to a transportation accident in Seattle

- Emerging Scientific Advances and Their Implications for Security by Dr. Casagrande of Gryphon Scientific

Memoranda of Understanding (MOU) have been established with the following groups to collaborate on preparedness efforts:

- ASBMT since 2006
- Department of Health and Human Services – Office of the Assistant Secretary for Preparedness and Response (HHS-ASPR) since 2007
 - This MOU was noted in the DHS Nuclear/Radiological Incident Annex to the Response and Recovery Fed. Interagency Operational Plans (Page 69)
 - https://www.fema.gov/media-library-data/1478636264406-cd6307630737c2e3b8f4e0352476c1e0/NRIA_FINAL_110216.pdf
- AABD-Disasters Task Force since 2008
- European Group for Blood and Marrow Transplantation - Nuclear Accident Committee (EBMT-NAC) since 2011

Additionally, the RITN maintains informal relationships to increase awareness about RITN worldwide through close interaction with:

- Biomedical Advanced Research and Development Authority (BARDA)
- Health Resources and Services Administration (HRSA)
- World Health Organization - Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN)
- Radiation Emergency Assistance Center and Training Site (REAC/TS)
- Armed Forces Radiobiology Research Institute (AFRRI)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institutes of Health (NIH) - National Library of Medicine (NLM) - Radiation Emergency Medical Management (REMM)
- American Hospital Association (AHA)
- Association of State and Territorial Health Officials (ASTHO)
- National Association of City and County Health Officials (NACCHO)
- Veteran's Administration Health System
- Centers for Medical Countermeasures Against Radiation (CMCR)
- National Security Council staff
- National Alliance for Radiation Readiness (NARR)



RITN uses Health Care Standard[®] (HCS[®]) software to consolidate participating hospitals Capability Reports and to communicate situation status updates to the network through a web based interface. Annual tests are conducted to ensure that users are familiar with the system and that it is capable of receiving and consolidating submitted data. This system allowed RITN to

collect the bed availability and on-hand G-CSF quantities throughout the network during a prior grant period.



The Assistant Secretary for Preparedness and Response from the Department of Health and Human Services has been a partner since the foundation of RITN. This partnership is formalized through an MOU and is prominently displayed on the Department of Health and Human Services website for Public Health Emergencies on the Chemical, Biological, Radiological, Nuclear and Explosive Branch page, (<http://www.PHE.gov/about/oem/cbrne>, and Figure 8):



Figure 8. Chemical, Biological, Radiological, Nuclear and Explosive Branch webpage noting the partnership with RITN.

NMDP's critical functions must remain operational during contingency situations that directly affect the Coordinating Center.

Operational Continuity Planning (OCP) is essential for world-class organizations to meet the myriad of 21st century emergencies; this is evident by the visibility of many standards, such as ISO 22301:2012 which specifies requirements to plan, establish, implement, operate, monitor, review, maintain and continually improve a documented management system to protect against, reduce the likelihood of occurrence, prepare for, respond to, and recover from disruptive incidents when they arise. The OCP is comprised of plans, systems, and processes for resuming NMDP operations in the shortest time possible following a severe operational disruption. OCP focuses on increasing the resiliency of the staff essential to conduct recovery operations, the facilities required to house these staff members, and the specialized long lead time equipment needed to connect these staff members to our data center from remote locations.

The OCP mitigates the effect of the many incident categories that may adversely impact NMDP operations. The OCP does not specifically plan for each possible hazard to the organization, rather it has a broad scope with a flexible and scalable response to allow for a successful activation in response to various catastrophic events ranging from fires, flooding, pandemics, extended evacuations (due to building damage, local chemical spill, or other hazards making the facilities unusable), to extended service outages such as water, electricity or sewer services. The OCP does not include NMDP Data Center incidents, as these are covered by the Information Services department through the Disaster Recovery program. NMDP continues to annually test its OCP to validate functionality with the continually changing information system environment as well as the growing organization structure and operational complexity.

The NMDP requires specialized technical staff to accomplish the organization's mission. The technical skill sets required are not readily replaceable. Without these staff members, the NMDP would not be able to support its network of centers in their daily operations and research programs. The NMDP OCP outlines procedures to allow resumption of operations within 72 hours of a catastrophic disruption. This is essential for the HCT community that relies on NMDP staff and systems for timely access to critical graft sources.

Development of Science and Technology for Rapid Identification of Matched Donors

Increasing the resolution and quality of the HLA testing of volunteers on the Registry will speed donor selection.

Increased diversity of newly recruited donors

During the NMDP's FY17, funding for NMDP donor centers (including DoD) and recruitment groups recruited 55,996 minority race and 164,691 Caucasian donors for a total of 220,687 U.S. donors added to the registry (25.4% minority).

Advancing technology improved performance and pricing

The NMDP typing strategy maximizes the use of funds by utilizing new typing methodologies that deliver a higher resolution of results at a lower cost than previous methods. The overall goal is to ensure that new donors are listed on the registry with the best possible resolution and number of loci tested. This is particularly critical during times of a contingency where well HLA-characterized adult donors must be readily matched to patients in need of HCT for ARS.

- In January of 2016 we began typing over 50% of new donors with NGS whole gene/long range (WG/LR), providing allele level, phased results. Between January 2017 and July 2017, 94% of newly recruited donors were typed with this methodology at HLA-A, B, C, DRB1, DQB1, DPB1, DRB3/4/5, ABO/RhD, and the CCR5 delta 32 mutation. From August 2017 through October 2017, 99% of newly recruited donors were typed with WG/LR. This method requires a DNA sample with minimal degradation, as can be found on a fresh buccal swab (<90 days of age). Samples that are >90 days of age are tested using the less stringent NGS Targeted Exon method, providing a minimum of G Group resolution (i.e. antigen recognition site sequence).

Enhancing Non-HLA data for selected donors

Transplant centers utilize donor CMV status and blood type (ABO/Rh) as non-HLA selection factors when multiple equally well matched donors are available. Historically, the only process to obtain this information is to request the potential donor on behalf of the patient, obtain a fresh blood sample, and perform infectious disease testing panel which includes the donor blood type and presence/absence of circulating antibodies to CMV. CMV antibodies are present in oral transudate fluid, in addition to blood serum. Over the course of several experiments, 2 different NMDP contract laboratories have been able to satisfactorily use a modified assay to test for the CMV virus when flocked swabs were used to collect oral specimens. The most recent study achieved both 100% positive predictive values and assay specificity, as well as >85% assay sensitivity and negative predictive values, when a small percent (<9%) of results were excluded as equivocal. Incorporation of this testing, in parallel with the HLA testing, of registry members at the time of recruitment, would provide a presumptive CMV serostatus to enhance the non-HLA information available and aid the Transplant Center with optimizing donor selection. The

next steps will evaluate if this data is associated with higher transplant center utilization along with a financial analysis of the additional costs of the test.

ABO/Rh at Recruitment by DNA-based testing

Due to recent advances in testing methodology (primarily due to NGS), it became feasible to explore adding ABO/RhD as another locus that could be tested from the same sample at the same time as recruitment HLA testing. The NMDP made sets of 1000 blind samples available to two laboratories for validation testing. A high degree of concordance between genetic ABO/RhD result and known serological ABO/Rh was seen for both sets (>97% concordance). DNA-based ABO/RhD testing on a portion of recruitment samples began in August, 2014. As of October 01, 2014, all recruitment samples receive ABO/RhD testing along with HLA testing as noted above.

Quality of HLA typings improved

The NMDP's comprehensive quality control program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. Blind Quality Control (QC) samples are added to each weekly shipment of new donor recruitment samples and any additional shipments that meet the minimum requirements. These QC samples comprise 2.5% of each shipment and are indistinguishable from the other samples. There are more than 800 QC Masters in active rotation, representing over 95% of common well-documented (CWD) HLA alleles. In order to maintain a robust and diverse inventory of QC Master samples into the long term future, a program to obtain samples from Registry donors with desirable HLA types and other unique immunogenetic factors has been developed and currently in the pilot phase of the program. Additionally, a software application has been developed for business users to manage QC sample inventory and test result management. This will allow staff to track sample age, document sample lineage, and detect patterns in reporting errors in real time. The application is fully functional, but there is an enhancement underway to enhance the discrepancy comparison logic for new test results received in comparison to the expected typing results.

Primary DNA typing data can be used within the Registry to improve the quality and resolution of volunteer donor HLA assignments.

An HLA assignment obtained by SSOP, DNA-based testing methods is derived from the positive and negative hybridizations of oligonucleotide reagents that define the presence of specific nucleotide sequences. Using this information and a list of known HLA alleles with their primary sequences, the typing laboratory interprets the hybridization results into possible allele combinations (interpreted data). The information for which polymorphic nucleotide sequences are present or absent is termed "primary data." Similar primary data are available from other DNA-based methods, sequence specific primers (SSP) and sequence-based typing (SBT).

The following poster abstracts were presented at the 2017 EFI meeting

- Maiers M, Michael Halagan M, Wang W et al. Community resources for automated annotation of HLA, KIR and beyond
- Milius RP, Schneider J, Brown A, et al. HLA and the EMR: Developing HL7 FHIR tools for exchanging NGS-based HLA genotyping

Data Standards Hackathon

Following three successful Data Standards Hackathons (DaSH) in DC, California and Minneapolis during a prior grant period, we organized three Hackathon events in the past year including two in Europe.

DaSH 4, Vienna, November 2016

This meeting was co-hosted by Gottfried Fischer, the previous president of European Federation for Immunogenetics, and took place at the University of Vienna. Forty coders and scientists attended, including 17 people from Europe.

DaSH 5, Berkeley, CA, March 2017

This meeting was co-hosted by Jill Hollenbach (UCSF) and Steve Mack (CHORI). 35 coders and scientists attended.

DaSH 6, Heidelberg, Germany, May 2017

This meeting was co-hosted by Hans-Peter Eberhard (ZKRD). 24 coders and scientists including 13 people from Europe.

DaSH 7, Utrecht, Netherlands, Nov 2017

This meeting was hosted by GenDx and 39 attendees from industry, academia and donor registries. The meeting focused on a number of topics:

1. Modeling peptide processing and presentation pathways (NetChop/Chipper, NetMHC), NeoAntigen Prediction, Whole Genome Sequence Analysis
2. HL7-FHIR: Tools for conversion of HML to FHIR bundles, FHIR Clinical Genomics, & Sync for Genes
3. Tools to support analysis of whole gene sequencing of HLA and KIR. These include Gene Feature Enumeration (GFE), Feature Service and the Allele Calling Tool (ACT).
4. Analysis of Primate MHC data using 17th IHIWS Informatics tools

5. Haplotype Frequency Curation. This is a new web service being develop to make haplotype frequency data from global populations available programmatically to software that consumes this frequency data (e.g. to make matching predictions).

There have been over 100 DaSH participants so far from CHORI, UCSF, Stanford and UC Berkeley, UCLA, the National Marrow Donor Program (NMDP) in Minneapolis, Children's Hospital of Philadelphia (CHOP), and the Department of Defense Marrow Program; the German Marrow Donor Program (ZKRD), the Center for International Blood and Marrow Transplant Research (CIBMTR), the Anthony Nolan Bone Marrow Trust (UK), the University of Vienna, and Maastricht University. Corporate participants include NGS platform vendors Illumina (San Diego), Pacific Biosciences (Mountain View) and Roche Molecular Solutions (Pleasanton); NGS software vendors Omixon (Prague), GenDx (Leiden), Immucor (Norcross, GA), ThermoFisher (Waltham, MA), and CareDx (Brisbane); and bioinformatics developers Knowledge Synthesis (Berkeley).

The work has focused on two main areas.

- Data standards for HLA: specifying principles for annotation and testing out data formats, tools and service with producers and consumers working together to provide rapid assessment. The goal is to develop a public “ecosystem” which is a set of tools and standards to create a shared facility for the storage, exchange and analysis of HLA and KIR data, project related data, and analytic results building on Minimal Information for Reporting Immunogenomic NGS Genotyping (MIRING), Histoimmunogenetics Mark-up Language (HML) and GL-service.
- HL7 FHIR (Fast Healthcare Interoperability Resources): exploring the use of HL7 as a convenient platform for exchanging HLA typing data, particularly by providing the code to test messages, as well as trouble shooting any problems in the data message exchange. This also included work on CCR5 and ABO/Rh reporting, and preparing a new HML schema to support nested specifications like FHIR.

HL7 (Health Level 7) Genomics

New and emerging technologies force the development of new and emerging standards. For example, the immunogenomics NGS community has recently developed a set of principles describing MIRING. However, these guidelines are not implementable using currently available data standard formats. Our approach has been to go forward in developing a technical implementation of the MIRING guidelines by extending HML (v0.3.3 to 1.0), and at the same time work with the larger genomics community standards being developed (Global Alliance for Genomics and Health, ClinGen) and healthcare interoperability standards communities HL7. By working with these communities, we are able to inform the development of new standards informed by MIRING principles and HML 1.0 specifications.

While HML 1.0 meets our current needs for reporting NGS based genotyping, it is not yet poised to interoperate seamlessly with clinical electronic medical record systems (EMRs).

We propose to evolve HML so that the next major version (HML 2.0) will be based on HL7 FHIR and should more easily integrate with EMRs.

The primary activity towards this goal in the past year has been:

1. Development of HL7 FHIR Profiles for HLA and KIR reporting through participation in the HL7 Clinical Genomics (CG) Work Group. Two FHIR profiles are under development:
 - An HLA typing report Profile using the existing NMDP HLA data collection form (Form 22) as a template. FHIR resources depend heavily on terminology binding. To support this project, an HLA Terminology Service is being developed that will adhere to HL7 FHIR API specifications for Terminology Services (<https://hl7.org/fhir/terminology-service.html>). This service for code systems used by the NMDP to describe HLA typings. The *post-coordination* concept aligns with other usage of coded HLA types, such as slash-delimited allele lists and GL strings.
 - MIRING compliant NGS-based genotyping report Profile. The HL7 Clinical Genomics Workgroup recently published a Standard Profile for Genetics for inclusion into the HL7 FHIR Standard for Trial Use 3. This Profile contains a specific provision for HLA reporting.
2. Working with vendors to include HML 1.0 and newly developed HL7 FHIR resources into their products.
 - EPIC – currently developing FHIR capabilities (<https://open.epic.com/Interface/FHIR>)
 - CareDx – They have joined the HL7 Clinical Genomics Work Group and are involved the development of FHIR resources and profiles for reporting HLA.
3. Informing the larger genomics communities of the unique needs of HLA and KIR. This includes participation with the data modeling efforts of Global Alliance for Genomics and Health, and the ClinGen Allele Data Model.

HML FHIR Converter

We developed a web server for converting HML messages into bundles of HL7-FHIR resources in order to demonstrate the conformance of HL7-FHIR clinical genomics resources with the complex MIRING principals and HML schema. This system is based on the HLA reporting bundle strategy in the FHIR genomics implementation guidance [document](#). Resources used

included Sequence, Specimen, Organization, Patient, Bundle, and the clinical genomics profiles (Observation, DiagnosticReport, DiagnosticRequest, HLA Genotyping Results).

Our software has been made available publically with separate [server](#) and [client](#) repositories.

We are continuing to validate this approach with HLA typing vendors at the Data Standards Hackathon (DaSH) events. As part of the Nov 2017 DaSH event, commercial partners (CareDx, GenDx, Omixon) started to test uploading HLA typing reports to a FHIR server hosted by NMDP. We continue to promote this approach with HLA typing and integration software vendors because it will facilitate better integration with Electronic Medical Records (EMR) software and allow HLA sequence information to be brought closer to the physician for more informed decision making.

Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor or cord blood unit.

HLA allele and haplotype frequencies are central to matching and the selection process as well as for more strategic tasks such as modeling registry growth or estimating match rates beyond the typing resolution of the donors in the registry.

Global HapLogic

We have developed a prototype implementation of HapLogicSM that applies global population frequencies developed under previous years of this grant to assigning match predictions to all donors and CBUs in the Bone Marrow Donors Worldwide (BMDW) database for display in the upfront search of Be The Match. This system is undergoing validation and haplotype frequency development.

Modeling Coverage Gaps in Haplotype Frequencies

We developed a method for addressing the problem that, due to the heavy-tailed frequency distribution of HLA haplotypes, computational methods that use this data often have to deal with rare haplotypes that have not been observed in the reference frequencies. Matching algorithms like HapLogic, for instance, face this situation on as many as 25% of the donors. Current methods for addressing this situation are crude – resorting to individual allele frequencies to make predictions. We developed a Bayesian inference method for extending haplotype frequency distributions using a model where new haplotypes are created by recombination of observed sub-haplotypes. This method preserves linkage disequilibrium information in smaller haplotype components and has been shown to provide improved prediction over previous methods. The method has been published a paper titled: “[Modeling coverage gaps in haplotype frequencies via Bayesian inference to improve stem cell donor selection](#)”.

Multi-race Bayes

We have further developed and validated a method for imputing HLA using a Bayesian framework where the a subject's HLA was imputed and the most probable continental origin (Africa, Asia, etc.) was assigned to the subject's haplotypes. This method was applied to a cohort of 110,000 donors who participated in study that collected geographical ancestry information by questionnaire and compared the results to the HLA and the self-identified race. The results are being prepared for publication but the main finding is that the combination of self-identified race and geographical ancestry combined provide more information and correlate better with HLA genetics than either variable on its own.

Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.

Donor Match Rate Studies

Temporarily Unavailable Donor Contact Project

In this project, donors with a TU status (temporarily unavailable) with an available date (i.e. data at which transplant centers (TCs) can request donor for activity) in the following month who are best/only for a searching patient are identified. The donor is contacted and provided with detailed messaging about their importance to the patient. At that time, their willingness to proceed once their TU date expires is assessed. If they are not interested in proceeding they are deleted from the registry and this information is provided to the transplant center in the event they were waiting for this donor prior to pursuing other therapeutic options. If the donor commits to being available once their TU date expires they are given a health history questionnaire and given further information on the process, as needed. This information is also communicated to the transplant center.

This project began in March, 2017. Table 3 shows the number of donors and availability rate of after contact to confirm they are able at the end of the TU period. Since March, 107 donors have been contacted with

30 (28%) available when their TU date expired, to date. Twelve of these available donors have been requested for the patient. One donor went on to donate stem cells for a patient and a second donor is scheduled for donation at the end of December.

Table 3. TU Donor contact project results

Donors contacted	107
Donors available	30
TU date extended	20
Deleted	28
Duplicate donor	1
Donors contacted	41
Donors available	11
TU date extended	4
Deleted	17
Pending	8
Duplicate donor	1

Selection, Typing and Transplant (STaT)

Patients transplanted earlier in their disease cycle are associated with better outcomes and better chance at survival. The median time from preliminary search to donor workup is over 100 days, potentially putting patients at higher risk for relapse and disease progression in addition to additional cost and morbidity due to the additional need for immune therapy (chemotherapy and/or radiation). Haploidentical transplant numbers continue to increase, potentially as a result of the perceived increased time and cost associated with unrelated donor transplant. Transplant centers may be using less desirable haploidentical donor (per treatment protocols) because of slow delivery of unrelated donors.

The STaT study is aimed to determine the feasibility of identifying a suitably matched unrelated donor in an expedited timeframe (14 days). The goal is to decrease the overall timeline to transplant for urgent patient cases and allow clinical decisions to be made with the full complement of stem cell product choices available for best treatment of the patient

The study has enrolled patients from 2 different transplant centers and currently ready to add 2 more transplant centers. The study has enrolled 43 patients and 9 collections completed (7 more scheduled) with the median day from selection to transplant 68 days. NMDP delivered a WU ready donor in 14 days or less nearly 90% of the time. The majority of the patients not meeting the 4-6 week transplant target were delayed due to a patient related issues.

Rapid identification of potential donors for newly diagnosed AML patients

The Southwest Oncology Group (SWOG) has identified the time from diagnosis of Acute Myelogenous Leukemia (AML) to transplant as critical for successful treatment of patients with cytogenetically defined high risk disease. Proceeding to transplant within four months of

diagnosis for patients with high risk disease in first chronic remission could potentially improve the overall disease free survival rates. Currently, these patients are referred for transplant following cytogenetic screening and several lines of therapy. The initial diagnosis and treatment phase can take several months significantly delaying the initiation of an unrelated donor search and making transplant within four months highly unlikely. NMDP/CIBMTR up front involvement would permit the rapid identification and pre-search screening of potential donors, so patients will be well along in the search process when/if ultimately referred for HCT.

In April 2013 SWOG initiated the clinical trial entitled, [*“S1203: A Randomized Phase III Study of Standard Cytarabine plus Daunorubicin \(7+3\) Therapy or Idarubicin with High Dose Cytarabine \(IA\) versus IA with Vorinostat \(IA+V\) in Younger Patients with Previously Untreated Acute Myeloid Leukemia \(AML\)”*](#). The trial was a randomized phase III trial of cytarabine and daunorubicin hydrochloride or idarubicin and cytarabine with or without vorinostat to see how well they work in treating younger patients (18-60 years old) with previously untreated acute myeloid leukemia. Drugs used in chemotherapy, such as cytarabine, daunorubicin hydrochloride, idarubicin, and vorinostat, work in different ways to stop the growth of cancer cells, either by killing the cells or stopping them from dividing. Giving more than one drug (combination chemotherapy) and giving the drugs in different doses and in different combinations may kill more cancer cells. It is not yet known which combination chemotherapy is more effective in treating acute myeloid leukemia. The study included a transplant arm for patients diagnosed with high risk cytogenetics following the initiation of induction therapy (see Figure 9 below). NMDP/CIBMTR supported the project using grant funds to provide study-specific sample collection kits for all enrolled patients, processing samples, HLA typing patients that were diagnosed as cytogenetic high-risk and generating preliminary search strategy reports to assist in the identification of donors and/or CBUs through the NMDP. The resulting search information was provided to the S1203 transplant arm principal investigator who shared the data with the referring physician.

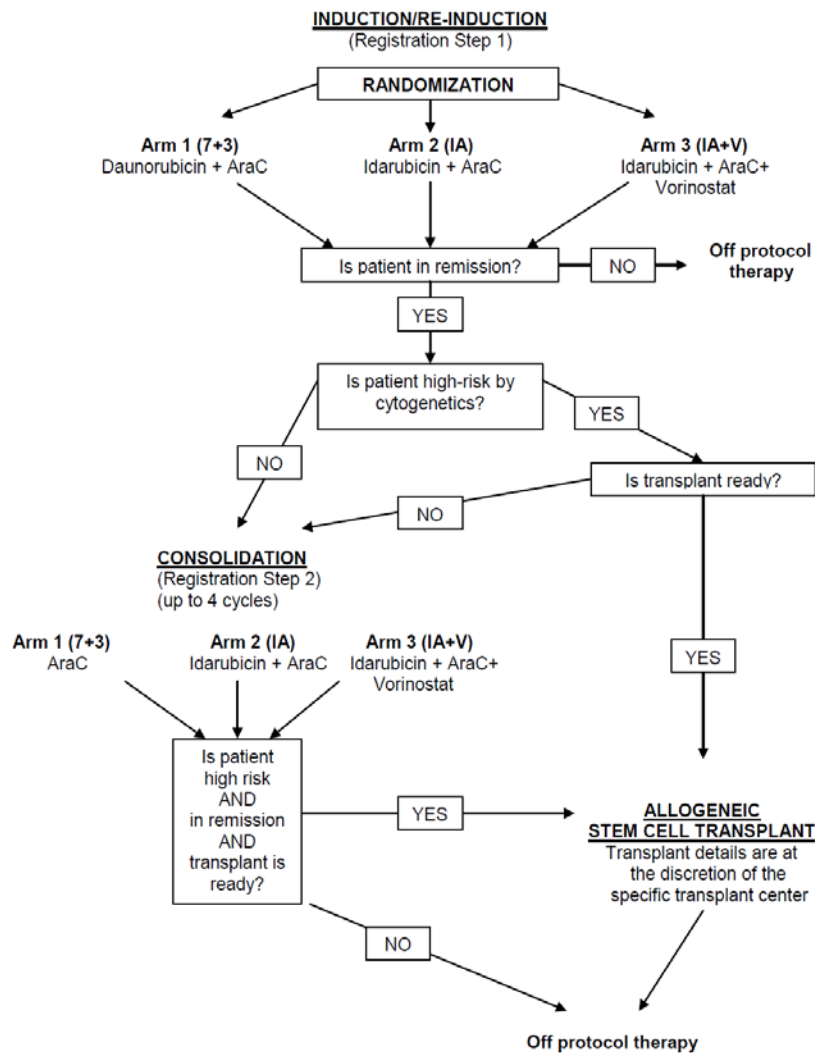


Figure 9. S1203 trial randomization and treatment schema.

The study opened in April 2013 and accrual was completed November 2015. The results of the transplant cohort was reported as an oral abstract at the 2016 ASH annual meeting. Of 738 eligible patients (median age, 49 years; range, 18-60), 159 (22%) had high-risk cytogenetics, of whom 60 (38%), 61 (38%), and 38 (24%) received induction with 7+3, IA, or IA+V, respectively. A total of 107 of the 159 high-risk patients achieved complete remission (CR1) (67%). HCT was performed in 317 of all 738 patients (43%) and 68 (64%) of the high-risk patients received a transplant in CR1 ($p < 0.001$ compared to historical rate of 40%). Twenty-five (37%) had a matched related donor, 31 (45%) had a matched unrelated donor, 3 (4%) had a mismatched related donor, 8 (12%) had a mismatched unrelated donor, and 1 (1%) received an umbilical cord blood transplant. Median time to HCT from CR1 was 76 days (range, 20-365). Fifty-seven patients (86%) received a myeloablative regimen and 9 (14%) reduced-intensity

conditioning. Reasons for 39 high-risk CR1 patients not receiving a transplant in CR1 were: co-morbidities (n=1), death (n=6), no insurance (n=1), no donor (n=1), physician decision (n=3), patient decision (n=3), relapse (n=6), other (n=10), or unknown (n=8). The 2-year relapse-free (RFS) estimate in the entire high-risk cohort is 32%, significantly higher than the 22% historical rate ($p=0.05$). Median RFS in the high-risk CR1 cohort (n=107) was 10 months [range, 1-32* (censored) months]. RFS and overall survival (OS) were similar among HCT patients using matched related [1 year estimates: 40% (95% confidence interval (CI) 27%, 74%) and 56% (37%, 74%), respectively] and matched unrelated [1 year estimates: 52% (37%, 75%) and 56% (37%, 74%), respectively] donors in CR1. The HR (reference = unrelated) for RFS was 0.67 (0.32, 1.37) and for OS was 0.88 (0.41, 1.90). Median overall survival (OS) among all patients in the high-risk cohort (n=159) was 12 months [range, 1-33* (censored) months] and was 18 months [range 3-33* (censored) months] for those transplanted in CR1 (Figure 10). The study clearly demonstrated that in newly diagnosed adults with AML age 18-60, early cytogenetic testing with an organized effort to identify a suitable allogeneic HCT donor led to a CR1 transplant rate of 64% in the high-risk group, which in turn led to a significant improvement in RFS over historical controls. Better outcomes in poor prognosis AML patients may be achieved simply by rapidly finding unrelated donors and performing allogeneic HCT in CR1 as soon as possible. The manuscript is in progress and will be submitted in 2018.

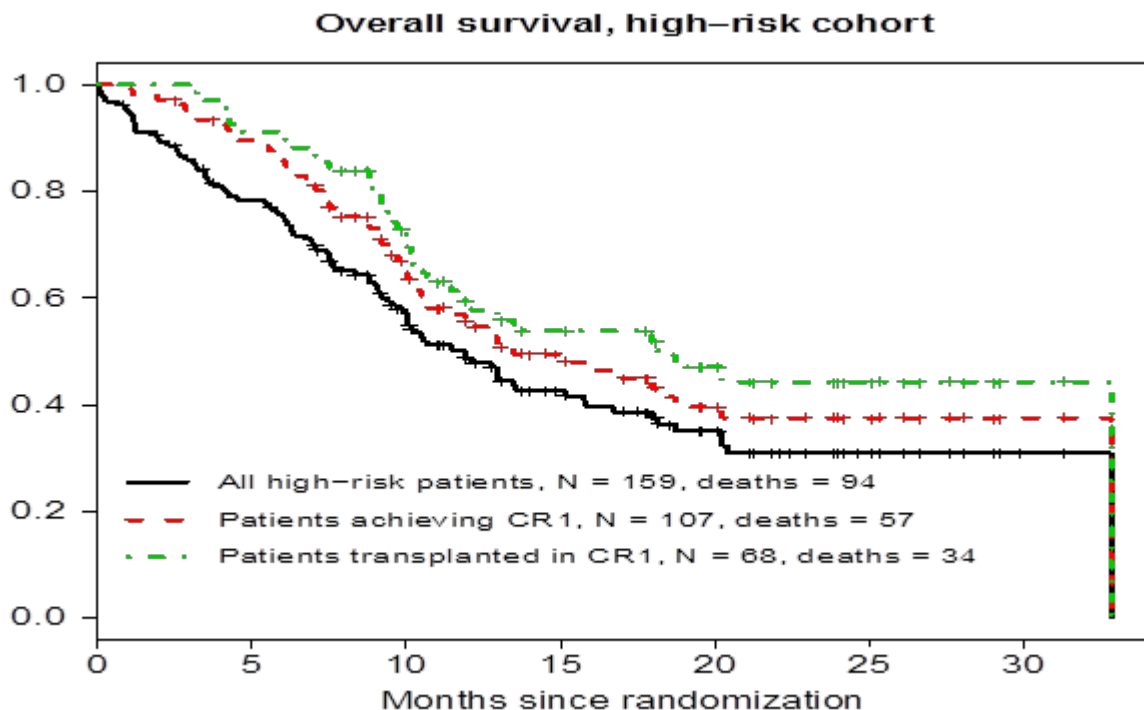


Figure 10. Overall survival of high risk cytogenetic AML patients enrolled in SWOG 1203.

Immunogenetic Studies in Transplantation

HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations, it will not be possible to delay transplant until a perfectly matched donor can be found.

Donor/Recipient Pair Project

A retrospective Donor/Recipient Pair HLA typing project to characterize class I (HLA-A, B and C) and class II (HLA-DRB, DQB1, DQA1, DPA1 and DPB1) alleles of stored donor/recipient paired samples was initiated in 1994. To date, over 30,000 unrelated paired samples and more than 1,991 related paired samples from the Repository have been fully characterized and the resultant data are available for research use. The data are stored in an NMDP developed database and is available to any researcher with a CIBMTR approved study wishing to analyze the impact of matching as either the focus of, or as a variable in a research study. To date, 171 published research studies (not including abstracts) have used these data describing the importance of high resolution HLA matching in unrelated donor transplantation that formed the basis for NMDP's updated guidelines for unrelated adult donor HCT HLA matching.

During this reporting period, HLA and KIR typing labs were contracted to type 3619 unrelated donor transplant pairs for the project. All samples were typed using NGS methodologies at a minimum of G group resolution. After successful completion of the typing, each pair was audited for use in analyses. All samples were selected in collaboration with the CIBMTR Statistical Center to ensure the additional cases would benefit ongoing and future analyses. Transplantation practices are constantly evolving and the project will continue to enroll the most recent transplant pairs to ensure that changes in practice can be evaluated with fully quality controlled high resolution HLA data. With the implementation of the IPR database, we continue to audit sample groups that contain both KIR and high resolution HLA to allow for inclusion in studies.

Full HLA Gene Typing Match Assessment

The impact of amino acid differences outside of the antigen recognition domain (ARD) have not been previously evaluated in a retrospective analysis. During a prior grant period, a collaborative project was launched with the research laboratory at the Georgetown University Medical Center to generate complete HLA gene sequencing at HLA-A, B, C, DRB1, DQB1 and DPB1 on a cohort of previously characterized ARD identical at HLA-A, B, C, DRB1 and DQB1 unrelated donor/recipient pairs from the CIBMTR Research Repository.

A pilot cohort of 360 pairs were analyzed to assess the frequency of sequence disparities outside of the ARD and facilitate a sample size calculation for the final study cohort. The majority of the population was self-identified Caucasian (80%). NGS was performed on the Illumina MiSeq

platform and interpreted with Connexio Assign MPS. Class I gene sequences covered 5'UTR-3'UTR; DRB1, intron 1-intron 3; DQA1 5'UTR-exon 4; DQB1, intron 1-3'UTR. DQ noncoding regions were not evaluated. The majority (98.1%) of the pairs were matched for sequences outside the ARD exons: 0.5% differed in non-ARD exons, 1.9% differ in noncoding regions. A small number (0.2%) differed within ARD exons. Mismatches in non-ARD exons varied from 0.7% for HLA-C and DQA1 to 0% DQB1; noncoding variation ranges from 2.8% for HLA-C to 1.3%, HLA-B and DRB1. Within non-ARD exons, both nonsynonymous (16 allele pairs) and silent (2) variation were present. Intron variation was minor and usually impact only a single nucleotide (Figure 11).

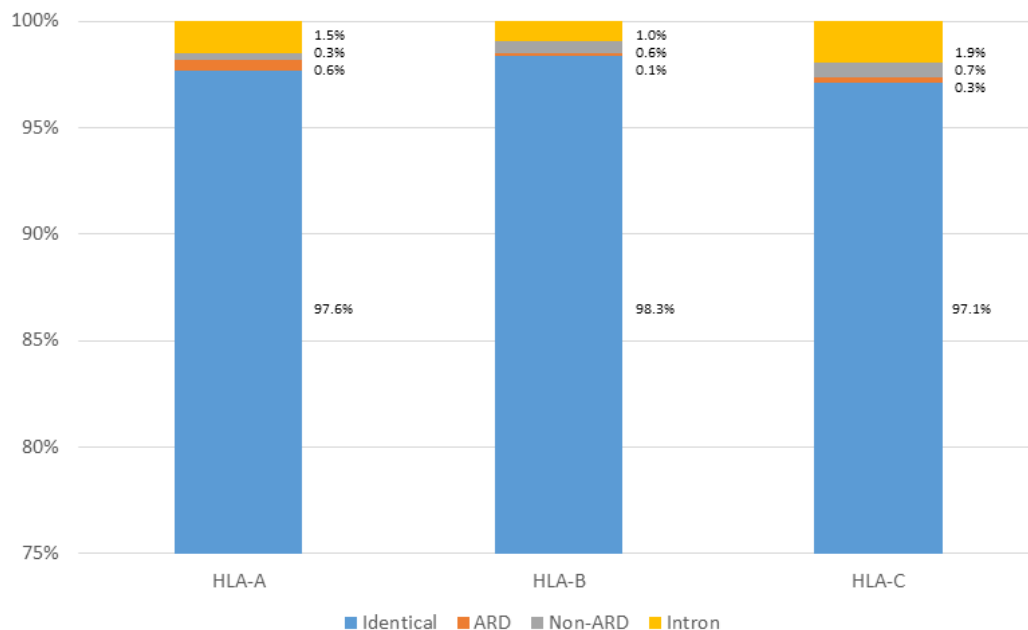


Figure 11. Summary of HLA class I matching between unrelated donor and recipient by locus. The four categories include: (1) donor and recipient carry identical alleles (exons and introns); (2) donor and recipient exhibit a difference in the exons encoding the ARD; (3) donor and recipient exhibit a difference in the non-ARD encoding exons; and (4) donor and recipient exhibit a difference in an intron. Each histogram represents 720 allele comparisons.

This was the first study to evaluate the genetic variation and characterize mismatching outside of the ARD in a cohort of HLA-matched donor-recipient pairs. The paucity of exonic mismatches outside of the ARD is striking. Intronic variation was more common but would not contribute to an alloreactive mismatch as these variants are not present in the final protein. At present, it does not appear to be necessary to increase the resolution of HLA typing beyond the ARD in selecting a matched donor except in cases of common non-expressed variants within G-group assignments. The impact of amino acid sequence variation caused by substitutions in exons outside ARD regions in donor-recipient pairs will be difficult to assess in HCT outcome studies since it does not occur very frequently. Further study is warranted to confirm these findings in larger and more diverse cohorts. The results of the study were presented as oral abstract and received an ASHI Scholar award during the 2016 ASHI annual meeting. The results were summarized in a manuscript and was published in HLA.

During this reporting period, the study was extended to a larger cohort that includes over 4,700 pairs tested through the Donor/Recipient Pair Project. Sequence variation annotation is in process and expected to be completed in early 2018.

Analysis of whole genome sequence data

We developed a computational pipeline to identify Minor Histocompatibility Antigens (MiHAs) that integrates data from donor/recipient pair whole genome sequences and HLA genotypes and published information on tissue-specific expression and documented MiHAs to predict new MiHAs. Analysis of 205 transplant pairs resulted in a number of potential MiHAs including a set of X-Y chromosome markers where mismatching between markers on the Y-chromosome of male patients and the paralogous genes on the X-chromosome of female donors was associated with acute Graft versus Host Disease (aGvHD). An abstract describing the computational method was presented at the ASHI annual meeting (Sept 11-15, 2017 in San Francisco) with the title : “MiHAP: Comprehensive Pipeline to Discover Immunogenic Minor Histocompatibility Antigens via Whole Genome Sequences of HLA-matched Donor-Recipient Pairs”. The software is [available](#) publicly.

17th International Histocompatibility and Immunogenetics Workshop (IHIW) collaboration

The NMDP collaborated with the IHIW KIR component to produce multiple replicates of a panel of 10 KIR defined reference samples from the pool of previously expanded high resolution KIR typed cell lines at the CIBMTR Research Repository. This panel was used to qualify laboratories for participation in the IHIW KIR sequencing project. Laboratories received either DNA or viable cell lines as requested. The samples were selected for haplotypic diversity and alleles with large insertions and/or deletions. We received presence absence typing from 7 of the 9 typing

labs and CNV typing from 4. We have also started a collaboration with the DKMS typing laboratory in Dresden to confirm the allelic typing on 40 NMDP KIR high resolution typed reference cell lines. The results will be analyzed in the next quarter.

Antigen Recognition Domain (ARD) study

Amino acid mismatches outside the ARD (i.e., exons 2 and 3 for HLA class I and exon 2 for class II) are ignored under current HLA matching guidelines with the assumption that these differences are irrelevant. There is little data to confirm or refute this assumption; furthermore, the amount of data needed to form a conclusion is unattainable. In order to provide more information, the ARD allo-reactivity assessment project will provide insight into the allowable percent tolerance of matching needed outside of the ARD. It is collaboration between the NMDP and Eurodonor under the direction of Machteld Oudshoorn and Franz Claas from Leiden, Netherlands.

Initial investigation of the Class II ARD mismatch of DRB1*14:01 and DRB1*14:54 and DRB3*02:01 and 02:02 respectively have produced preliminary results demonstrating two weakly positive and one positive result. Interestingly, all positive results occurred in one direction only, which is DRB1*14:01 / DRB3*02:01 against DRB1*14:54 / DRB3*02:02. This data from the Class II analysis was presented in an oral abstract²⁷ at the 2013 EFI conference in Maastricht, Netherlands. To confirm these results, we identified 135 additional donors via registry queries. Fresh blood draws were collected from 22 donors and peripheral blood mononuclear cells cryopreserved for evaluation. All combinations tested showed no responses in the mixed lymphocyte culture whereas 4 out of 10 combinations were positive in the Elispot against the combined DRB1/DRB3 mismatch and only in one direction; DRB1*14:01/DRB3*02:01 against DRB1*14:54/DRB3*02:02. Positive responses were confirmed by primed lymphocyte testing (PLT) that was more sensitive than the Elispot. Furthermore, the PLT results suggested that the DRB1* mismatch was responsible for the response. In conclusion, mismatches involving positions outside the ARD are not very immunogenic. However, some mismatches can lead to T cell reactivity in vitro. The impact of these mismatches on clinical outcome of HCT remains to be established. The study results were submitted to Bone Marrow Transplantation and accepted with minor revisions.

Analysis of four HLA Class I ARD mismatches; A*02:01 and 02:09, B*44:02 and 44:27, C*07:01, 07:06 and 07:18 have demonstrated that the selected pairs do not travel on the same haplotypes. A manuscript describing these results has been submitted to the Journal of Human Immunology for publication.

Even when patient and donor are HLA matched, GVHD occurs, therefore, other loci may play a role.

A poster abstract was presented at the ASHG annual meeting in Vancouver, BC in October 2016.

- Madbouly A, Besse K, Wang Y, et al. Insights into the Geographical Distribution of genetic admixture of Unrelated Volunteer Donors and Recipients of Stem-Cell Transplants

A poster abstract was presented at the Neoantigen Summit in Boston, MA in November 2016.

- Wei W, Udell J, Huang H, et al. Identification of Minor Histocompatibility Antigens Based on Whole Genome Sequencing of 205 Donor-Recipient Pairs

Table 4 lists currently active and completed CIBMTR/NMDP-supported studies that are conducted on NMDP samples. The CIBMTR/NMDP encourages such collaborative projects and closely monitor them. Such studies are instrumental to understanding the role of non-HLA loci in HCT. The data is obtained and generated via NMDP donor and recipient research samples, along with their outcomes and demographics. The researchers are required to submit the interpreted results of all assays performed on the samples. The data submission requirement ensures that all sample testing yields information that is readily available to the HCT research community for subsequent analysis and eliminates or reduces duplicative testing to preserve resources and sample inventory. These results are stored in the IPR and IIDB databases, and associated with their samples in the CIBMTR Research Repository database.

Non-HLA data is available for use in research studies in a fashion analogous to the Donor/Recipient Pair Project generated HLA data and is made available, when possible, via the NMDP Bioinformatics web site. Data origin will be noted for all information stored, along with relevant citations. Access to the detailed data will be subject to the existing NMDP/CIBMTR data request procedures.

Table 4. Immunobiology typing projects utilizing NMDP samples and contributing data to the IPR database

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
NK Cells, Their Receptors and Unrelated Donor Transplant	J. Miller	2300 pairs	KIR	RT-PCR, FACS, SSO, MALDI-TOF	Yes
Survey of Diversity of Immune Response Genes in Unrelated Hematopoietic Stem Cell Transplantation	C. Hurley	40 Pairs	cytokine and KIR	SBT	Yes
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic GVHD	R. Abdi	1300 pairs	CCL1, CCL2, CCR5, CCR2, CX3CR1	Taqman PCR	Yes
Functional Significance of Killer Ig-like Receptor (KIR) Genes in HLA Matched and Mismatched Unrelated HCT	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes
Functional Significance of Cytokine Gene Polymorphism in Modulation Risk of Post-Transplant Complications	E. Petersdorf	2500 pairs	>30 Immune response genes	Taqman PCR	Yes
Identification of Functional SNPs in Unrelated HCT	E. Petersdorf	3500 pairs	Entire MHC region	Taqman PCR	In Process
Use of Female Donors with Pre-existing Antibody to H-Y Antigen will Result in Robust Serologic Response to H-Y Antigens in Male HSC transplantation Recipients	D. Miklos	288 pairs	H-Y Antigen	ELISA, protein array	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Multiplexed Genotyping of Human Minor Histocompatibility Antigens (mHAg): Clinical Relevance of mHAg Disparity in Stem Cell Transplantation	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor- α : Prognostic significance in Allogeneic Stem Cell Transplantation	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation	L. Baxter-Lowe	102 pairs	HLA	SBT	Yes
Detection of HLA Antibody in Single Antigen HLA-Mismatched Unrelated Donor Transplants	S. Arai, D. Miklos	200 pairs	Anti-body	ELISA, Protein array	Yes
Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Stem Cell Transplantation and Their Relationship to Graft/Patient Outcome	R. Bray	111 pairs	Anti-bodies	Flow cytometry	Yes
Genome-wide Association in Unrelated Donor Transplant Recipients and Donors: A Pilot Study	R. Goyal	858 pairs	> 600,000 Genome wide SNPs	Human 610 - Quad V1 arrays	Yes
SNPs in the p53 Pathway and Outcomes in URD HCT	B. DuPont	1500 pairs	p53, ATM, MDM2 and p21/Waf1	Taqman	In process
Association of Donor and Recipient Gene Polymorphisms of Drug and Innate Immune Response with Outcomes after URD HCT	V. Rocha	725 pairs	GSTP, GSTT, GSTM, UGT CD14, TIRAP, and NALPs	Taqman	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
To Develop and Test a Prognostic Index for Survival in CML URD HCT	1. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of TGF- β 1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A	R. Shah	400 samples	TGF- β 1	Taqman	Yes
Donor and Recipient Telomere Length ^{47, 48} as Predictors of Outcomes after Hematopoietic Stem Cell Transplant in Patients with Acquired Severe Aplastic Anemia	S. Gadalla	650 samples	Telomere length and Telomerase Polymorphisms	Taqman	Yes
Development of a GVHD Prevention Bidiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	Yes
Genetic polymorphisms and HCT related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT	T. Hahn	>4,000 pairs	GWAS	Array	In process
Impact of CTLA4 SNPs on outcome after URD transplant	M. Jagasia	1,200 pairs	CTLA-4 SNPs	Taqman	Yes
KIR genotyping and immune function in MDS patients prior to unrelated donor transplantation	E. E. Warlick and J. Miller	970 samples	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	Yes
Plasma YKL-40 and CHI3LI genotype to predict mortality after unrelated donor HCT	2. Kornblit	800 pairs	YKL-40 plasma levels and CHI3LI SNPs	ELISA and Taqman	Yes
Natural killer cell genomics and outcomes after allogeneic transplantation for lymphoma	V. Bachanova, J. Miller, D. Weisdorf and L. Burns	800 pairs	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Effect of genetic ancestry matching on HCT outcomes	A. Madbouly, M. Maiers and N. Majhail	2300 pairs	Ancestry Informative Markers	Taqman GWAS	Yes
Impact of MHC Class I chain related polymorphisms on HCT outcomes	M. Askar and R. Sobecks	700 pairs	MICA genotypes	Taqman	Yes
Prognostic impact of somatic mutation and the levels of CXC chemokine ligands in MDS	W. Saber, R.C. Lindsley and B. Ebert	1300 pairs	Chemokine levels Somatic mutations	ELISA Sequence capture	Yes
Mitochondrial DNA haplotypes and outcome	M. Verneris and J. Ross	4000 pairs	SNPs	Taqman	Yes
Assessing T cell repertoire similarity in HLA mismatched HCT	E. Meyer	50 samples	TCR repertoire sequence	NGS	In process
Impact of SNPs in the Gamma Block of the MHC	M. Askar and R. Sobecks	700 pairs	SNPs	Taqman	Yes
Clinical outcomes among HCT recipients as a function of socioeconomic status and transcriptome differences	J. Knight, J.D. Rizzo and S. Cole	252 samples	Gene expression array	Array	Yes
Natural killer cell genomics and outcomes after HCT for CLL	V. Bachanova, J. Miller, D. Weisdorf and S. Cooley	600 samples	KIR genotype	SSP	Yes
Donor telomere length and outcomes after HCT for acute leukemia	S. Gadalla, S. Savage, D. Loftus and E. Hytopoulos	1145 samples	Leukocyte telomere length	qPCR	Yes
KIR gene content and pediatric acute leukemia HCT outcome	M. Verneris, J. Miller and S. Cooley	500 samples	KIR genotype	SSP	In process
Functional genetic variants of the ST2 gene in pairs of recipient and donors for risk stratification of GVHD and TRM outcomes.	S. Paczesny and S. Spellman	1000 pairs	sST2	Taqman	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
The role of HLA-E compatibility in the prognosis of acute leukemia patients undergoing 10/10 HLA matched HCT	C. Tsamadou, D. Furst and J. Mytilineos	3300 pairs	HLA-E	NGS	In process
Donor-Recipient NK cell determinants associated with survival in JMML after HCT	D. Lee, H. Rangarajan	465 pairs	KIR	NGS	In process
Identification of genomic markers of post-HCT outcomes in patients with myelofibrosis	W. Saber, S. Gadalla	393 samples	Somatic mutations	Taqman	In process
Epigenetic profiling of URD donor/recipient pairs to improve donor selection for HCT	S. Beck, K. Peggs, V. Rakyan, A. Webster	288 pairs	DNA methylation	EPIC array	In process
Impact of telomere length and telomerase gene mutations on allogeneic stem cell transplantation in myelodysplastic syndrome	C. Lindsley, I. DeVivo, S. Agrawal, D. Neuberg	1300 pairs	Telomere length and telomerase gene mutations	RT-PCR Taqman	In process

Clinical Research in Transplantation

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Clinical Outcomes Research

Clinical Outcomes Research using the CIBMTR Research Database is a core activity of the organization. These studies address a wide range of issues, focusing on questions that are difficult or impossible to address in single center studies or randomized trials because diseases treated with HCT are uncommon, single centers treat few patients with a given disorder, and not all important questions are amenable to a randomized research design. The majority of the clinical outcomes research is conducted through the CIBMTR Working Committee structure, which incorporates many highly successful researchers in clinical transplantation. The Working Committees perform retrospective studies to identify the most promising transplant approaches, and by identifying the patients most likely to benefit from this therapy. In addition, research in immunobiology was conducted to better understand how transplantation works including how to harness the power of the immune system to control cancer.

The CIBMTR collects data for approximately 22,000 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. Figure 12 shows cumulative accession of transplants since 1970 when the International Bone Marrow Transplant Registry began collecting these data and figure 15 shows the distribution of graft source by donor type. These data are the basis for the CIBMTR Clinical Outcomes Research program and are accessed by the Working Committees to conduct studies.

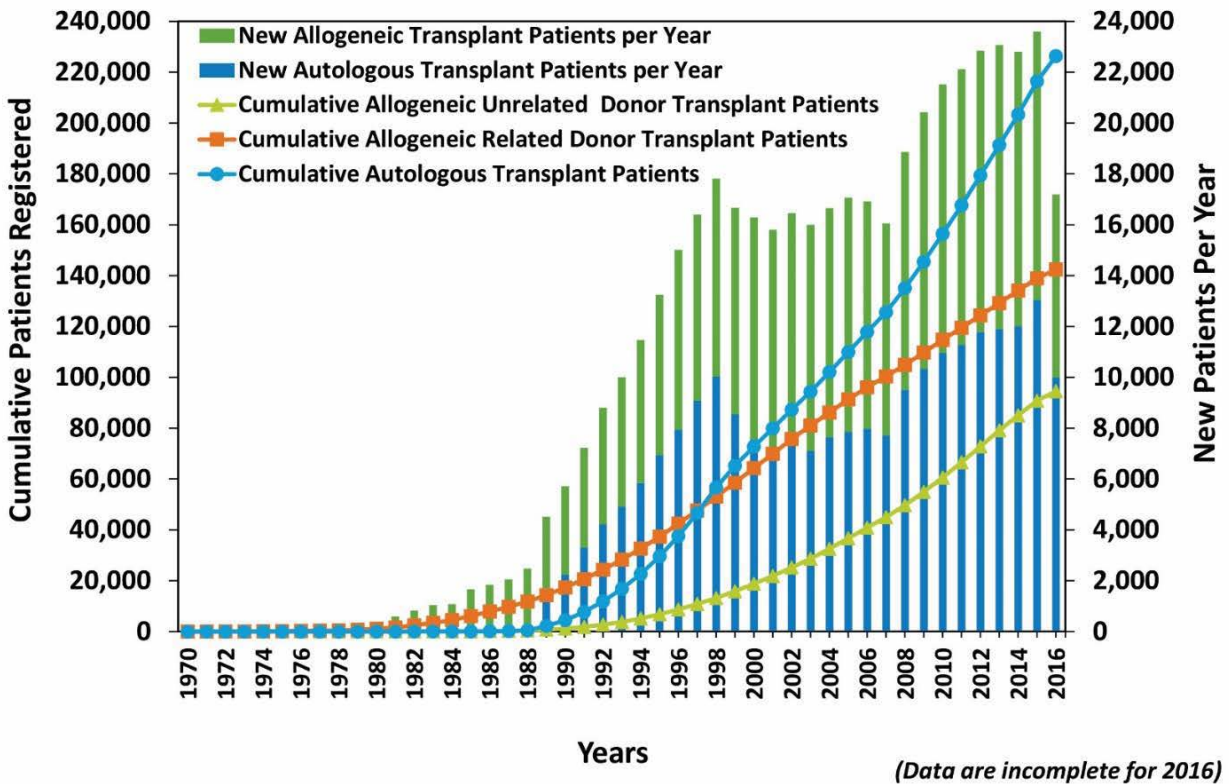


Figure 12. Accession of Transplant Recipients Registered with the CIBMTR

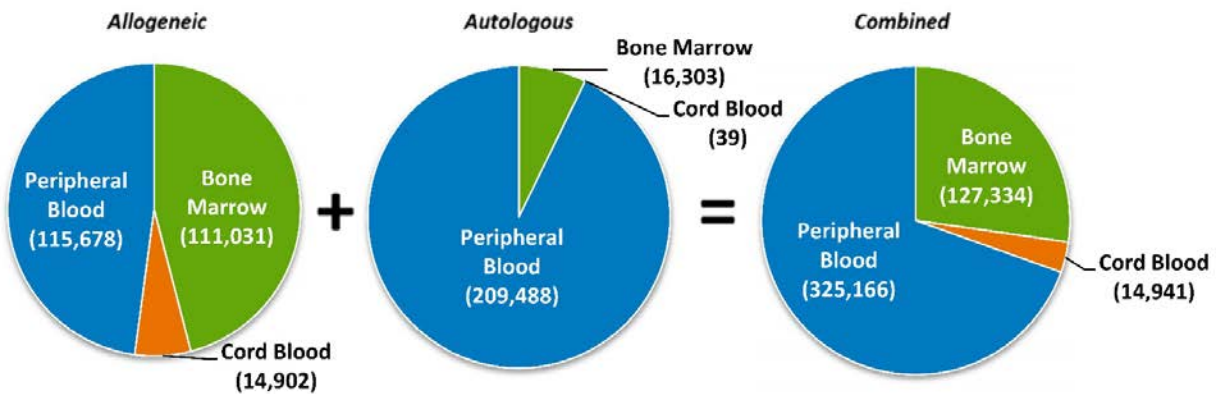


Figure 13. Distribution of Patients in the CIBMTR Research Database by Graft Source

Currently, there are 15 Working Committees within the CIBMTR with 176 active studies in progress (Table 5). In 2016, the CIBMTR published a total of 95 mostly peer-reviewed publications (66 working committee studies, 1 Health Services Research, 14 BMTCTN, 5 Statistical Methods and 9 Bioinformatics) (Figure 14). Publication data for 2017 will be reported in the annual report for this grant. Sources of funding for these studies vary by investigator, but the majority use NMDP resources and CIBMTR statistical support. In addition, the CIBMTR received 205 new study proposals and accepted 78 for discussion at the February 2017 ASBMT/CIBMTR BMT Tandem Meetings. The CIBMTR received 204 new study proposals

and accepted 97 for discussion at the February 2018 ASBMT/CIBMTR BMT Tandem Meeting. Proposals can be dropped for various reasons including; feasibility, low scientific impact, overlap with existing studies or combined with other proposals due to overlapping hypotheses. Ten abstracts were submitted and accepted for presentation (8 oral and 3 poster) at the 2016 BMT Tandem Meetings. Seven abstracts were submitted and accepted for presentation (4 oral and 3 poster) at the European Blood and Marrow Transplant Group Meeting. Twenty one abstracts were submitted and accepted for presentation (9 oral and 12 poster) at the ASH meeting in December 2017. The CIBMTR

Table 5. 2016 CIBMTR Working Committee portfolio and productivity

Working Committee	Studies in Progress	Publications	Presentations
Acute Leukemia	14	5	2
Autoimmune Diseases and Cellular Therapies	5	0	0
Chronic Leukemia	12	5	1
Donor Health and Safety	11	2	2
Graft Sources and Manipulation	7	5	1
Graft-versus-Host Disease	10	1	2
Health Services and International Studies	11	7	3
Immunobiology	39	12	13
Infection and Immune Reconstitution	7	5	0
Late Effects and Quality of Life	11	8	3
Lymphoma	9	4	1
Pediatric Cancer	5	0	1
Plasma Cell Disorders and Adult Solid Tumors	9	5	4
Primary Immune Deficiencies, Inborn Errors of Metabolism, and Other Non-Malignant Marrow Disorders	14	2	0
Regimen-Related Toxicity and Supportive Care	12	5	2
TOTAL	176	66	35

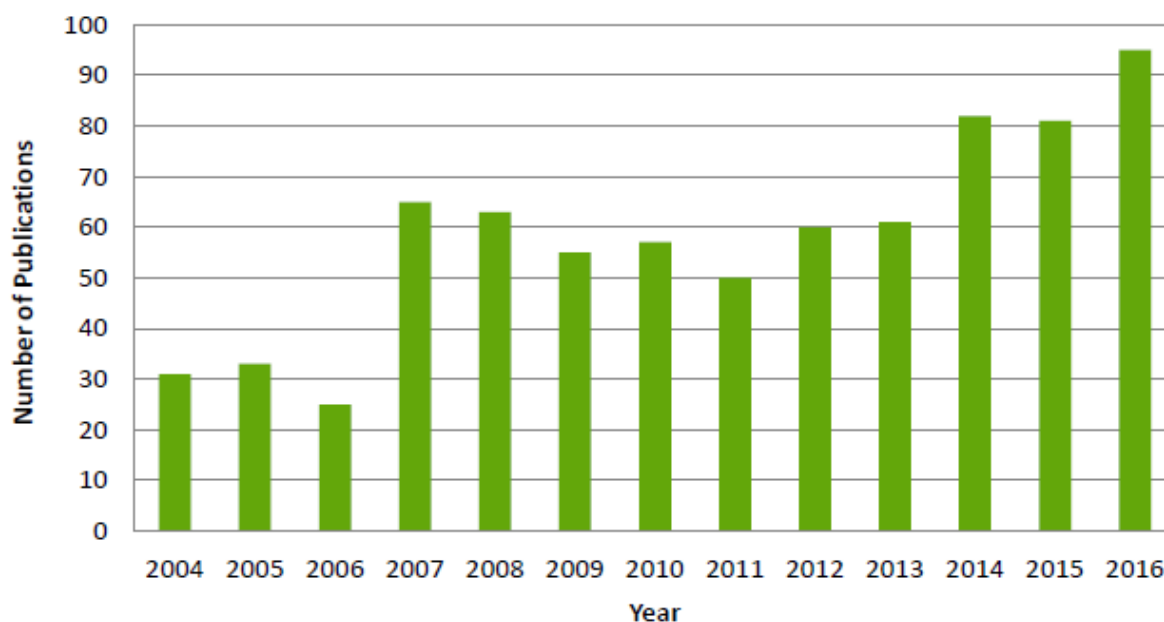


Figure 14. CIBMTR peer-reviewed publications by year.

Prospective research

In 2017 CIBMTR began planning and development of an electronic Patient Reported Outcomes (ePRO) system for patients to contribute PRO data directly to clinical trials and other CIBMTR research. When implemented the system will integrate Qualtrics as a patient-facing ePRO interface with Salesforce as the client relationship management system used by the Survey Research Group and deliver PROMIS measures using computer adaptive testing (CAT) technology. PROMIS are person-centered measures that evaluate physical, mental and social health and are supported by a NIH initiative. During this year, CIBMTR has selected vendors and reviewed the system design with our Architecture Review Board, information security team, and enterprise project management office. The system development and implementation is planned for 2018 and will be funded under a separate grant.

The Survey Research Group continued to conduct donor follow-up assessments for the Long Term Donor Follow-up study. During the project period the team completed > 7,800 LTDFU assessments with donors.

Cord Blood Research Initiatives

During the project period, the Cord Blood Research Sub-advisory Group met semi-monthly to discuss study priorities and plan analyses for the following:

NMDP Cord Blood Access (10-CBA) Protocol Clinical Results

Umbilical cord blood transplantation (UCBT) is an important option for patients, including those of diverse race/ethnicity, without a matched donor. The FDA began licensure of UCB units in 2011. Fewer than 5% of UCB units are licensed; therefore, the NMDP facilitated UCBT under IND: “A Multicenter Access and Distribution Protocol for Unlicensed Cryopreserved Cord Blood Units for Transplantation in Pediatric and Adult Patients with Hematologic Malignancies and Other Indications.” The CIBMTR analyzed and presented outcomes of 1589 patients undergoing UCBT using unlicensed units at the 2017 BMT Tandem meetings as a poster. Engraftment and overall survival were excellent for the diverse patients receiving UCBT using these unlicensed units. Incidence of neutrophil engraftment (ANC > 500) at Day 42 was 88%, 89%, and 92% for adults, pediatric-malignant disease (PediM), and pediatric non-malignant disease (PediNM) respectively (Figure 15). Overall survival (OS) at 100 days/1 year was 82% and 55% for adults, 86% and 67% for PediM, and 92% and 79% for PediNM (Figure 16). The manuscript was submitted to JAMA for peer review in November 2017.

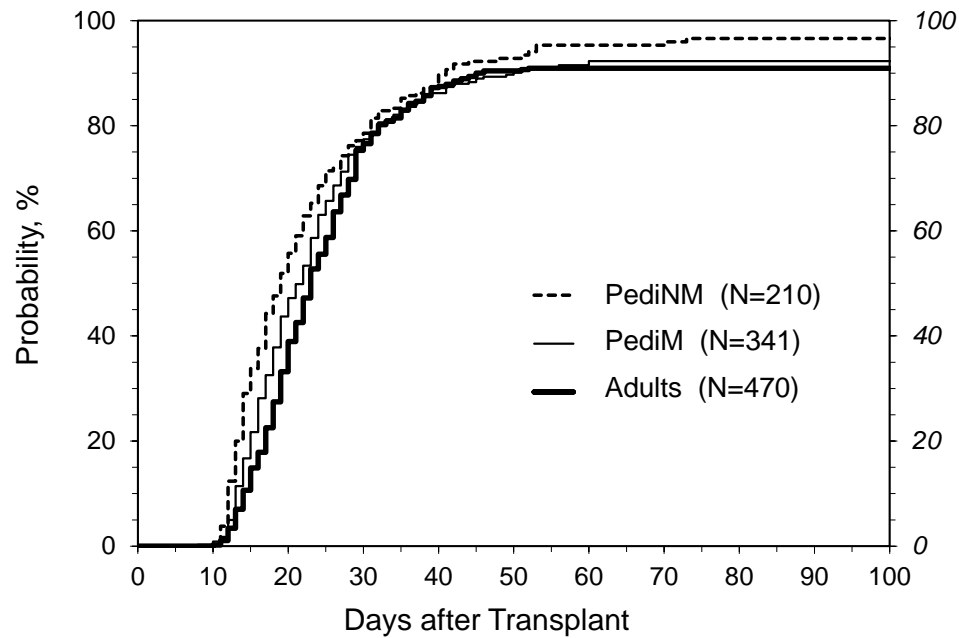


Figure 15. Neutrophil Engraftment after First Umbilical Cord Blood Transplantation (Myeloablative only)

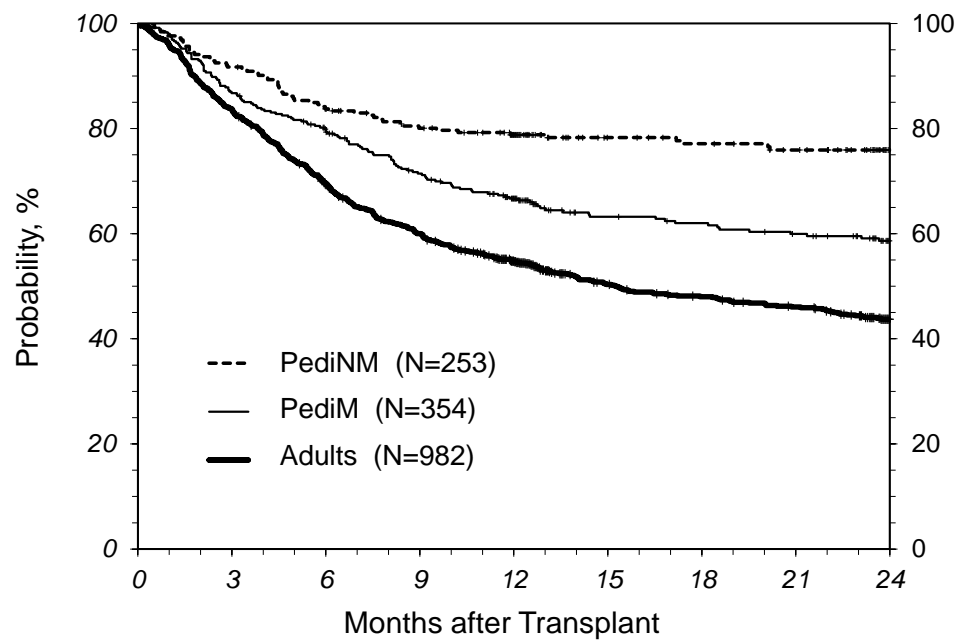


Figure 16. Overall Survival after First Umbilical Cord Blood Transplantation

Immunobiology Research

During a previous grant period, the NMDP developed the Immunobiology Research grant request and award procedures for use by the IBWC and developed the IBWC Web site (http://www.cibmtr.org/COMMITTEES/Working_Committees/Immunobiology/index.html). The content was further refined and migrated to the CIBMTR.org Web site in 2010 and is refreshed annually.

During the past grant period, the IBWC leadership attended the 2017 Cellular Therapy Forum and presented data on the benefits of collection and storage of biospecimens for correlative research. Support permitted the committee to maintain a strong performance record with 9 publications (submitted or accepted) since the last report. In addition, 4 new proposals were initiated by the IBWC in July 2017. The IBWC received 14 proposals for consideration at the 2018 BMT Tandem Meeting and will be presenting 8 for potential acceptance.

IBWC manuscripts since 2017 annual report (submitted/accepted):

1. IB13-01: Eapen M, Wang T, Veys PA, Boelens JJ, St Martin A, Spellman S, Bonfim CS, Brady C, Cant AJ, Dalle J-H, Davies SM, Freeman J, Hsu KC, Fleischhauer K, Kenzey C, Kurtzberg J, Michel G, Orchard PJ, Paviglianiti A, Rocha V, Veneris MR, Volt F, Wynn R, Lee SJ, Horowitz MM, Gluckman E, Ruggeri A. Allele-level HLA matching for umbilical cord blood transplantation for non-malignant diseases in children: A retrospective analysis. *Lancet Haematol* 2017 July 1;4(7):e325-e333. doi.org/10.1016/S2352-3026(17)30104-7. Epub 2017 June 13.
2. IB09-06/RT09-04b: Clay-Gilmour AI, Hahn T, Preus LM, Onel K, Skol A, Hungate E, Zhu Q, Haiman CA, Stram DO, Pooler L, Sheng X, Yan L, Liu Q, Hu Q, Liu S, Battaglia S, Zhu X, Block AW, Sait SNJ, Karaesmen E, Rizvi A, Weisdorf D, Ambrosone CB, Trichter D, Ellinghaus E, Ellinghaus D, Stanulla M, Clavel J, Orsi L, Spellman SR, Pasquini MC, McCarthy PL, Sucheston-Campbell LE. Genetic association with B-cell acute lymphoblastic leukemia in allogeneic transplant patients differs by age and sex. *Blood Advances*. 2017 Sept 8;1(20):1717-1728. doi.org/10.1182/bloodadvances.2017006023. epub 2017 Sept 12.

3. IB14-01: William BM, Wang T, Haagenson M, Fleischhauer K, Verneris M, Hsu KC, de Lima MJ, Fernandez-Vina M, Spellman SR, Lee SJ, Hill BT. Impact of human leukocyte antigen (HLA) alleles on outcomes of allogeneic transplantation for B-cell non-Hodgkin lymphomas: A Center for International Blood and Marrow Transplant Research analysis. *Biol Blood Marrow Transplant*. doi.org/10.1016/j.bbmt.2017.11.003. Epub 2017 Nov 16.

4. IB15-06a: Gadalla SM, Wang T, Loftus D, Friedman L, Dagnall C, Haagenson M, Spellman SR, Buturovic L, Blauwkamp M, Shelton J, Fleischhauer K, Hsu KC, Verneris MR, Krstajic D, Hicks B, Jones K, Lee SJ, Savage SA. Donor telomere length and outcomes after allogeneic unrelated hematopoietic cell transplant in patients with acute leukemia. *Bone Marrow Transplant*. doi.org/10.1038/s41409-017-0029-9. Epub 2017 Dec 21.

5. IB10-01d Flow Cytometry using FISH techniques in a Severe Aplastic Anemia population. Gadalla S, Aubert G, Wang T, Haagenson M, Spellman SR, Wang L, Katki HA, Savage S, Lee SJ. Submitted. *Blood*.

6. IB13-08 Prediction of Acute Graft-Versus-Host Disease Following Hematopoietic Cell Transplantation (Lee C, Haneuse S, Wang H, Rose S, Spellman SR, Verneris M, Hsu K, Fleischhauer K, Lee SJ, Abdi R) Submitted. *PLOS1*.

7. IB14-06 Donor-directed HLA-specific antibodies in unrelated hematopoietic cell transplantation for non-malignant disorders. Woolfrey A, Wang T, Lee SJ, Haagenson MD, Chen G, Fleischhauer K, Horan J, Hsu K, Tyan D, Verneris M, Spellman SR, Fernandez-Vina M. Submitted. *Blood*.

8. IB14-08 Development and validation of a clinical unrelated donor selection score. Shaw BE, Logan BR, Spellman SR, Marsh SGE, Robinson J, Pidala J, Hurley C, Barker J, Maiers M, Dehn J, Wang H, Haagenson M, Porter D, Petersdorf EW, Woolfrey A, Horowitz MM, Verneris M, Hsu KC, Fleischhauer K, Lee SJ. Submitted. *Biol Blood Marrow Transplant*.

9. IB15-06b Evaluation of a Machine Learning-Based Prognostic Model for Unrelated Hematopoietic Cell Transplantation Donor Selection. Buturovic L, Shelton J, Spellman SR, Wang T, Friedman L, Loftus D, Hesterberg L, Woodring T, Fleischhauer K, Hsu KC, Verneris MR, Haagenson M, Lee SJ. Submitted. *Biol Blood Marrow Transplant*.

IBWC studies initiated in July 2017:

1. The impact of HLA-DPB1 levels of expression on clinical outcomes in HCT. PIs: M Askar and M Fernandez-Vina
2. Identification of genomic markers of post hematopoietic cell transplantation outcomes in patients with myelofibrosis. PIs: W Saber and S Gadalla
3. Donor-recipient NK cell determinants associated with survival in JMML after hematopoietic stem cell transplantation. PIs: D Lee and H Rangarajan
4. Epigenetic profiling of unrelated donor-recipient pairs to improve donor selection during hematopoietic stem cell transplants. PIs: S Beck, K Peggs, V Rakyen, A Webster

IBWC 2018 proposals to be presented at BMT Tandem Meetings in Feb. 2018:

1. PROP1710-09 Clonal Mosaicism and HCT Outcomes in Patients with Acute Leukemia, Myelodysplastic Syndromes and Severe Aplastic Anemia (L Sucheston-Campbell/T Hahn/S Gadalla)
2. PROP1711-97 Imputation of KIR in genome-wide association study and the association of KIR-HLA with outcomes following alloHCT In AML and MDS (C Camacho-Bydume/L Sucheston-Campbell/S Leslie/K Hsu)
3. PROP1711-03 Effect of HLA phenotypes on long term GVHD risk (C Story/M Riches/P Armistead)
4. PROP1711-06 Role of HLA allotypes in determining CMV and leukemia specific outcomes in patients undergoing unrelated donor alloHCT (B Shaffer/R Sottile/R O'Reilly/K Hsu)
5. PROP1711-106 The Impact Of MHC Class I Chain-Related Gene A (MICA) 129 Polymorphism On CMV infection in Unrelated Donor Hematopoietic Cell Transplants (HCT) For Hematological Malignancies – Extension of Study IB13-05 (M Askar)
6. PROP1711-79 Evaluation of the impact of donor KIR genotype on outcome after unrelated donor transplantation in patients with myelodysplastic syndromes or secondary acute myeloid leukemia – Joint study with EBMT Chronic Leukemia Working Party (J Schetelig, N Kröger, M Robin)
7. PROP1711-128 Chromosomal aberrations and transplant outcomes in patients with inherited bone marrow failure syndromes (Y Wang/S Gadalla)

8. PROP1711-71 The impact of HLA class I risk alleles associated with AA Immune pathogenesis on allogeneic transplant outcomes in patients with severe acquired aplastic anemia

CIBMTR Information Technology (CIT) Minneapolis Initiatives

The scope of the work performed by the CIBMTR IT department in Minneapolis includes collecting and reporting outcomes data on all allogeneic transplantations performed in the U.S. (for the Stem Cell Therapeutic Outcomes Database (SCTOD), as required by U.S. law). U.S. transplant centers also voluntarily submit autologous transplantation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. As a result, and as reported in the CIBMTR 2016 Annual Report, the CIBMTR Research database now contains information on more than 475,000 patients. CIT strives to provide applications that will reduce center burden for government mandated forms and provide high quality data on demand.

CIT Application Suite:

- FormsNet: Recipient – Donor
- AGNIS
- Management Reporting
- Sample Tracking
- Auditing

FormsNet

Since its original release in Dec 2007, the Recipient Module of the FormsNet application has been used at more than 527 centers to register 214, 601 patients and collect over 1,741,961 forms with more than 10 million data elements. This program was developed for both local data entry from paper forms and web-based entry by clinical centers. More than 98% of data collected by the CIBMTR is submitted electronically via FormsNet. Two forms (2800 – log of appended documents and 2801 – transfer forms) can only be submitted on paper to ensure audit standards. The Form 2800 – log of appended documents, is in process of being decommissioned as a new feature has been added to FormsNet3 proving the ability to attach electronic documents directly to a form.

FormsNet 3.0 is CIBMTR's currently operational, 21 CFR Part 11 compliant, secure Web-based application for collecting hematopoietic cell transplant (HCT) outcomes data electronically. FormsNet supports data collection, auditing, and event reporting; donor clearance and follow-up; web services; and messaging. FormsNet offers real-time data validations; error messaging; and control of data entry flow, which includes enabling/disabling of questions and "smart navigation" between fields on a form. The system also collects information on non-HCT cellular therapies using a flexible design to accommodate therapies used independently, before or after HCT. The original deployment in December 2007 was built in 126,000 lines of code supporting

90 Recipient forms and no user tools. Today there are over 450,000 lines of code supporting 123 forms, tools, web services, email, and two user-based modules. Old revisions of Recipient and Donor forms are also still supported. The application is fully integrated with the CIT applications suite supporting CIBMTR. The application was converted from its original website to a web application with an enhanced object oriented code structure. Service Oriented Architecture integration services were created to provide flexibility and extensibility for future enhancements. In 2012, the planned upgrade to FormsNet replaced the technical foundation of the current FN2 application, with more agile, efficient & effective systems. It improved the user experience by providing enhanced functionality (defined by the network users). In 2014, the Donor module was upgraded to the FormsNet 3 platform, providing the same benefits for Donor module users as realized by Recipient module users. In 2015, CIBMTR evaluated and determined that an external Clinical Trials product will be purchased and integrated with the CIBMTR platform to meet the electronic data capture business need, as opposed to an upgrade of the FormsNet application to support this need. Utilizing non-Navy funding, in 2016 the Medidata RAVE package was implemented for use as the web-based electronic data capture system for Clinical Trials and other prospective research projects. RAVE also is the system used for monitoring of the data submitted.

In 2017, FormsNet was upgraded quarterly to keep Recipient forms current with existing treatment practices. Eighteen revised Recipient forms were released into production, along with 3 new Recipient forms. Platform enhancement continued, including migration of the remaining 3 tools requiring conversion to FormsNet 3 from FormsNet 2 platform.

Continued to support data collection for the Myelofibrosis Medicare study; four new forms needed to support this study were released in January 2017.

Cellular Therapies: In 2017, implemented five cellular therapy form revisions and 3 new forms needed to support a cellular therapies registry.

Transitioned Infectious Disease Marker results from FormsNet1 (FN1) to FormsNet3 (FN3) in order to correct regulatory deficiencies, improve operational efficiencies and allow for the import of electronic results.

FormsNet was updated monthly during 2017 to enhance the Recipient, Donor, and Audit modules to apply enhancements and ensure optimal performance, flexibility and efficiency of applications.

A Growable Network Information System® (AGNIS)

AGNIS is a system for electronic messaging of standard Common Data Elements (CDEs) between participating nodes. Messaging can occur between transplant centers, registries, investigators or any combination of entities willing to map relevant data elements and install the software/messaging system. The system relies on two key components, data standards in the form of common data elements (CDEs), and software for transferring the data, providing audit trails, conveying error messages, etc.

- **CDE Development:**
CIBMTR has invested substantial effort defining CDEs for CIBMTR forms. All CDEs are defined in the Cancer Data Standards Repository (caDSR) of the NCI. This leverages a strong national system of standards regarding the definitions and related metadata. Additionally, a substantial portion of the CDEs have also been defined in the Biomedical Research Integrated Domain Group (BRIDG) model, which is compatible with HL7, the most prevalent ‘language’ used in biomedical informatics.
- **Cancer Data Standards Repository (caDSR):**
 - In the caDSR, common data elements for FormsNet database fields are compiled into Form Builder reports, which convert CIBMTR format into caDSR format and which centers use to submit data automatically to FormsNet via AGNIS. To date, common data elements have been created for nearly than 22,200 FormsNet database fields. This represents those database fields associated with 99% of the forms submitted via FormsNet. In addition, 40 Form Builder reports have been released in the caDSR, 71 are pending quality assurance testing in AGNIS, and 9 are pending testing by AGNIS end-users.
- **Supported Forms:**
 - 12 recipient outcome forms are available for electronic data exchange via AGNIS: five mandated forms (pre- and post-TED, HLA, IDM, Infusion), three Comprehensive Forms (Baseline, Follow-Up, and Death), Unique ID Assignment, Indication for CRID Assignment, and two disease specific inserts (Pre- and Post-HSCT Hodgkin and Non-Hodgkins Lymphoma).
 - The data from four recipient outcome forms were combined into new revisions of existing forms. AGNIS supported this change, so while there is a fewer number of forms the amount of data collected is still the same.
 - Started developing 4 cellular therapy forms that will be supported by AGNIS in 2018
- **System Users:**
 - Independent Transplant Centers:
 - 5 centers actively submitting and retrieving data through AGNIS: H. Lee Moffitt, MD Anderson, Cleveland Clinic, Stanford, and Maisonneuve-Rosemont Hospital

- 2 center actively retrieving through AGNIS: Seidman Cancer Center and MD Anderson
- Transplant centers using Vendor solutions:
 - Eight vendor solutions supporting seventeen actively submitting centers and twenty-five retrieving centers
 - Liaison Technologies: One site submitting data
 - Management Science Associates: Three site submitting data
 - Mediware: Two sites submitting data
 - OTTR: Seven sites retrieving data
 - StemSoft: One site submitting data
 - StemTrek: One site submitting data
 - Jagriti: One site submitting data
 - Moffitt: One site submitting data (both a center and a vendor)
 - Velos: Six sites retrieving
 - TeleResults and Title21: authorized but not currently supporting centers
- System Enhancements:

In the last year, the AGNIS team accomplished the following:

- The AGNIS platform was used for over 26,000 submissions to FormsNet
- Provided ongoing support for EBMT-CIBMTR and CIBMTR-Eurocord AGNIS connections
- Released the new revisions of the 2400r5 Pre-Transplant Essential Data Form, 2402r1 Pre-Transplant Essential Data: Disease Classification Form, 2450r4 Post TED Form, 2100r4 100 Day Post-HSCT Data Form, 2005 HLA Form and 2900 Death Form
- Registry connections:
 - EBMT has been working with the CIBMTR to develop a pathway to share TED-level data from EBMT centers that also participate in the CIBMTR. Mapping has occurred for the Pre-TED, Post-TED at 100 days, Unique ID, and Infusion forms. Data submission, initially manually and now with automation for prospective data submitted for over 54 participating centers so far and plans continue to grow users
 - 8 centers with authorization to randomization to TED or CRF
 - 39 TED only centers
 - Received >73,000 forms in complete status from EBMT through the AGNIS submission process since the beginning of this project and over 30,000 in 2016
- Electronic Medical Records (EMR) connections:
 - CIBMTR worked with EPIC to integrate 51 standard CDEs into the BMT registration form in EPIC (BMT smartform).
 - Consists of HCT physicians and IT staff who are working to standardize data collection in the EMR to facilitate ease of data collection, consistent with national data standards, and submission for use of research

- Working with one EMR vendor (Epic) on development of data collection tools for the EMR that will use CIBMTR-defined data standards in the Cancer Data Standards Registry and Repository (caDSR) and Biomedical Research Integrated Domain Group (BRIDG); this project should serve to increase future interoperability of EMR systems with CIBMTR
- Developed three tools so far: aGVHD documentation flow sheet, cGVHD documentation tool, and BMT SmartForm

Information Management

The CIBMTR Information Management Strategy (IMS) project's main objective is to establish a comprehensive program for the management of data across the enterprise, turning the large volumes of data into a strategic asset supporting high value, sophisticated analyses. The Integrated Data Warehouse is the primary deliverable for this project. At delivery, the Integrated Data Warehouse will contain high quality, validated data readily available to researchers for immunobiology, outcomes, and other types of analyses. It will be the single source of truth of data that supports the diverse administrative and scientific needs of internal and external stakeholders. The team is building a unified domain to house multiple sources and dimensions of data. CIBMTR operational teams will be able to dramatically reduce the amount of time they spend on data consolidation, preparation, and validation of datasets and instead focus on the analysis. As a result, analyses will be completed in a timely manner facilitating decision-making based on these data assets.

- This effort is aligned with NMDP enterprise architectural standards, and incorporates selective use of industry standards, including BRIDG (Biomedical Research Integrated Domain Group) and HL-7 FHIR (Fast Healthcare Interoperability Resources). The first deliverable implemented an Integrated Data Store (IDS) which serves as the foundation for the long-term data warehouse. Using the IDS as the unified data source, the first phase of the Data Warehouse was completed by integrating data used for immunobiology analyses into the Data Warehouse. In FY17, the team completed the redesign of the architecture to more optimally support consolidation of data from various application sources as well as data and information provisioning to CIBMTR stakeholders, supporting future initiatives for faster, more flexible access to data. Accomplishments include: completion of the database design for the data warehouse, successful implementation of the physical model, including completion of loading a subset of CIBMTR data into the unified domain, proof of concept data extraction, and validation of the unified domain data extract against an existing comparable CIBMTR data set.
- As part of building the overall unified domain model, other accomplishments include:
 - Designing an Extract Transfer Load (ETL) process and translation scripts for loading data from the data sources into the unified domain.

- Began initial design for analytical extract model.
- Completed metadata mapping for proof of concept data.
- Developed roadmap for future data population and extract capabilities.

Table 6 below shows the types of data stored in the Data Warehouse and their data sources, including data sources added since the original release of the IDS:

Table 6. Types of sources of data in CIBMTR Data Warehouse

Focus area	Description	Source
IDM	<ul style="list-style-type: none"> • Donor IDMs information for NMDP facilitated HCTs 	Legacy (Formsnet1) & current FormsNet3
Infusion data	<ul style="list-style-type: none"> • 180 most Requested Variables for ad-hoc and center volumes reporting requests from FN3 • Clinical outcome data tied to each infusion event (future) 	FormsNet, SIP
NMDP Source Data	<ul style="list-style-type: none"> • Cord Blood Unit Data • Double Cord (Multi) 	StarLink CordLink (SyBase) CordSource through Reg ODS Emtrax through Reg ODS
HLA/KIR Match Data	<ul style="list-style-type: none"> • Transformed CIBMTR Legacy HLA data • HLA data for donor/recipient for NMDP facilitated HCTs, legacy and current (STAR/SIP) (form 2005) • HLA data transformation on new form 2005/non-NMDP Tx SCTOD data • Donor-Recipient Match Grade results (HLA Save) • KIR data • Re-Evaluate current data sources 	<ul style="list-style-type: none"> • CIBMTR OBS DB • STAR • FormsNet3 • IPR • HLA Save

Focus area	Description	Source
Donor & Recipient Data	<ul style="list-style-type: none"> Transformed Donor and Recipient data Provides self-service environment for analysis through pre-defined joins (business view of the metadata), calculations and generating adhoc data sets Capability for near real time(~ 5 minutes) data sharing and analytics across forms through combined and unified virtualization layer (views) Faster turnaround on visibility to data quality fixes. 	<ul style="list-style-type: none"> FormsNet NMDP Legacy
Metadata	<ul style="list-style-type: none"> Provides data lineage, impact analysis and FormsNet metadata analysis 	<ul style="list-style-type: none"> FormsNet Metadata, BODI metadata, OBIEE metadata
Center volumes	<ul style="list-style-type: none"> Provides metrics around the number of infusions by center/donor type/product type/disease/age group/race variables Replaces existing manual process 	<ul style="list-style-type: none"> FormsNet, NMDP
Repository Sample Data	<ul style="list-style-type: none"> Integration with 3rd party vendor, Labvantage, to provide Research Sample data Provides self-service environment for analysis through Business Intelligence tool. (OBIEE) Provides end user defined reports utilized to complete HRSA reporting requirements. 	<ul style="list-style-type: none"> FormsNet, Labvantage
IDM	<ul style="list-style-type: none"> Donor IDMs information for NMDP facilitated HCTs 	Legacy (Formsnet1) & current FormsNet3
Clinical Trials CT Rave	<ul style="list-style-type: none"> Integration with 3rd party vendor, Metadata Rave, to provide Clinical Trials data Provides self-service environment for analysis through Business Intelligence tool. (OBIEE) 	<ul style="list-style-type: none"> Rave, NMDP, FormsNet

Focus area	Description	Source
Audit	<ul style="list-style-type: none"> • Provide Business Intelligence environment (OBIEE) for internal Audit staff. • Provides end user defined reports and ad hoc analysis capabilities 	<ul style="list-style-type: none"> • FormsNet3
Cellular Therapy	<ul style="list-style-type: none"> • Storage of Cellular Therapy data collected FormsNet3 forms 	<ul style="list-style-type: none"> • FormsNet3

In addition to the referenced source data consolidated in the Data Warehouse, CIT has also implemented operational improvements to the warehouse, and developed, in the last 12 months, the following functionality:

- Data Quality Initiative: Data quality reporting dashboard has been developed and quality reports have been completed. Operational data quality checks and reports have been made available, allowing for early detection of questionable data in an effort to proactively identify and correct discrepant data, thus reducing the time spent preparing datasets
- Completed Data Warehouse Operational Improvements, including upgrades to the latest version of development tools and completion of automation of the Center Volumes Reporting Dashboard Data and Monthly Cord Blood Reports
- Enhancing the Business Intelligence application suite which shares data back with centers
 - Enhanced Data Back to Centers (eDBtC), which enables visualization of center trends and descriptive statistics as well as ad hoc querying capabilities, was enhanced with an extension to include the addition of 25 data dimensions and filters to enable development of ad hoc queries, as well as new functionality and data for visualization of sub-disease and GVHD prophylaxis.
 - Center Performance Analytics (CPA), which enables a center to analyze center trends related to other centers in data set, create selective queries, and export filtered data for analysis, was accessed 466 times by 93 unique center users.
 - Rolled out ASBMT for RFI (Request for Information) report, which Streamlines preparation of center's ASBMT Annual Request for Information – Outcomes Data Form. Since its launch, we estimate that Data for RFI represent approximately 328 distinct sessions and 43 unique users of those transplant centers accessing the eDBtC application. Additionally, we have received positive feedback from centers who have expressed that Data for RFI has simplified their ASBMT RFI reporting process.
- We extended the daily LabVantage data feed to the Integrated Data warehouse by bringing in additional variables. We also created an Adhoc reporting environment, enabling business users to obtain faster access to data by creating their own reports.

- Updated the regular data feed from the Clinical Trials software, Medidata Rave, to the Integrated Data Warehouse by including additional variables. We also created an Adhoc reporting environment, enabling business users to create their own reports and thereby obtain faster access to data.
- Completed a Survivorship report. This report is distributed on a weekly basis to Donor Centers to help track Survivor information. This report also eliminates dependency of legacy FormsNet form data to produce this report.

VI. Work plan

- a. Contingency Preparedness
 - Creation of web based just-in-time training on the care of Acute Radiation Syndrome patients while awaiting movement away from the disaster area and staying in austere conditions such as a field hospital or medical shelter.
- b. Development of Science and Technology for Rapid Identification of Matched Donors
 - Evaluate the factors of donor utilization and speed of search process after strategic upgrading of selected adult volunteer donors.
- c. Immunogenetic Studies in Transplantation
 - Complete HLA and KIR typing on additional donor/recipient transplant pairs to support evaluation of clinical studies of HLA mismatched transplants in an attempt to define tolerable mismatching in the unrelated donor HCT setting.
- d. Clinical Research in Transplantation
 - Provide analytical support for Immunobiology Working Committee research projects.

VII. Major Problems/Issues (if any)

No major problems encountered to date.

VIII. Technology Transfer

No technology transfer to report.

IX. Foreign Collaborations and Supported Foreign Nationals

NMDP has no sub awards with nor is it collaborating with any foreign entity or foreign national under this grant.

X. Productivity

a. Refereed Journal Articles

1. Hashmi SK, Bredeson C, Duarte RF, et al. National Institutes of Health Blood and Marrow Transplant Late Effects Initiative: The Healthcare Delivery Working Group Report. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*. 2017 May 1; 23(5):717-725. doi:10.1016/j.bbmt.2016.09.025. Epub 2016 Oct 3. PMC5378687.
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- b. Non-Refereed Significant Publications – None to report
- c. Books or Chapters – None to report
- d. Technical Reports – None to report
- e. Workshop and conference abstracts and presentations

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5. Bashey A, Hamadani M. Comparison of peripheral blood stem cells (PBSC) to bone marrow (BM) for t-replete HLA-haploidentical donor transplantation using post-transplant cyclophosphamide. ASH 2016.
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7. Qayed M, Horan J. Influence of age on risk for acute and chronic GVHD in children receiving HLA identical sibling bone marrow transplantation. ASH 2016.
8. Paulson K, Seftel M. Inferior access to allogeneic transplant in disadvantaged population: a CIBMTR analysis. ASH 2016.
9. Satwani P, Aplenc R. Role of donor source on clinical outcomes and inpatient resource utilization for hematopoietic cell transplantation in children with acute leukemia. ASH 2016.
10. Hahn T. Exome array analyses identify new genes influencing survival outcomes after HLA-matched unrelated donor blood and marrow transplantation. ASH 2016.
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21. Levine J, Harris A. Comparison of outcomes of myeloablative conditioning regimens combining busulfan with either cyclophosphamide or fludarabine in children. ASH 2016.
22. Strouse C. Stratification of allogeneic hematopoietic cell transplant patients by risk of developing veno-occlusive disease: a model for assigning a high-risk score. ASH 2016.
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42. Denzen E. Lessons learned from merging CIBMTR data and CMS medicare claims data. Tandem 2017.
43. Saber W. Stratification of allogeneic hematopoietic cell transplant patients by risk of developing veno-occlusive disease: a model for assigning a risk score. Tandem 2017.
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54. Prokopishyn N. Bone marrow transplant product quality has decreased over time. A retrospective examination of NMDP collected bone marrow products from 1994-2016. ASH 2017.
55. Fuchs E. Selecting between HLA-matched siblings and HLA-haploidentical related donors for acute leukemia in the era of post-transplant cyclophosphamid: The CIBMTR and Acute Leukemia Aorking party of the EBMT. ASH 2017.
56. Mehta R. Graft-versus-Host disease free relapse free survival and chronic GVHD in alternative donor hematopoietic cell transplantation in pediatric patients. ASH 2017.

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62. Norkin M. Late fetal infections remains frequent cause of mortality in pediatric allogeneic stem cell transplant recipients. ASH 2017.
63. Kumar S. Revised-international staging system is independently predictive and prognostic for early relapse after upfront autologous hematopoietic cell transplantation for newly diagnosed multiple myeloma. ASH 2017.
64. Kumar S. A comparison between 3 staging systems in multiple myeloma using the center for international blood and marrow transplant research database. ASH 2017.
65. Eikema R. Allogeneic hematopoietic stem cell transplantation in older patients aged 50 or older with severe aplastic anaemia: results from the european society for blood and marrow transplant and the center for international blood and marrow transplant research. ASH 2017.
66. Brunstein C. The effect of conditioning regimen dose reduction in obese patients undergoing autologous transplantation. ASH 2017.
67. Majhail N. Individualized treatment summaries and survivorship care plans for hematopoietic cell transplant survivors reduces cancer treatment distress in a randomized multicenter study. ASH 2017.
68. Medac. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndrome: effect of transplant conditioning regimen intensity on outcomes. ASH 2017.

69. Denzen E. Healthcare reimbursement and service utilization for one year of post-allogeneic hematopoietic cell transplantation care for medicare beneficiaries ages 65 and older with acute myeloid leukemia. ASH 2017.
 70. Murphy E. Individualized treatment summaries and survivorship care plans for hematopoietic cell transplant survivors reduces cancer treatment distress in a randomized multicenter study. ASH 2017.
 71. El-Jawahri A. What do transplant physicians think about palliative care? A national survey study. ASH 2017.
 72. Horowitz M. Nicord single unit expanded umbilical cord blood transplantation: Final results of a multicenter Phase I/II trial. ASH. 2017.
- f. Patents – None to report
 - g. Awards/Honors – None to report

XI. Award Participants

Employee name	Employee name	Employee name
Andrew Brown	Eva Chan	Madhuri Arikatla
Arnold Fritsch	Enoch Kan	Maria Brown
Andreas Hochrein	Emilie Love	Michael Haagensohn
Amy Ewer	Eric Williams	Michael Halagan
Abeer Madbouly	Eric Zink	Mamatha Kothamale
Abby McDonald	Gail Flickinger	Martin Maiers
Ashley Pull	Gretta Stritesky	Matthew Schmitt
Ashley Spahn	Harry Vassilev	Navitha Gargula
Andrew Westin	Caleb Kennedy	Nathan Hood
Shengchun (Ann) Zheng	Gideon Ogega	Pradeep Bashyal
Bill Burgess	Jennifer Bloomquist	Ray Hornung
Bob Milius	Jason Brelsford	Rupesh Kumar
Balu Samba	Jayesh Iyer	Stephanie Fingerson
Bridget Wakaruk	Jane Kempenich	Sharon Ewer
Chelsey Kornetzke	Jennifer Oakes	Shawn Freeman
Colleen Brady	Janelle Olson	Sreedhar Pasham
Cullen Case	Jane Pollack	Subhashini Samba
Charles Jordahl	Joel Schneider	Stephen Spellman

Cynthia Kunakom	Jacob Smith	Sean Stagg
Curt Mueller	Jen Venero	Srivani Vanteru
Cynthia Vierra-Green	Katherine Gee	Stephanie Waldvogel
Chia Yang	Kelli Olson	Thomas Wiegand
Daniel Campbell	Kirt Schaper	Tony Wirth
Dean Kloker	Kevin Tram	Vedavani Murukurthy
David McDonell	Kim Wadsworth	Venu Yarra
Denise Patrick-Johnson	Laura Clements	Alex Gomez
David Roe	Laura Gabrielson	Wei Wang
Dmitry Svito	Levi Moberg	Zubair Ahmed
Debra Turner	Lauren Schaerferle	